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HEMODYNAMIC CHANGES AND GUT BARRIER FUNCTION IN SEQUENTIAL PERIODS OF HYPOVOLEMIC AND ENDOTOXIC SHOCK

BY

DR. ROBERT G. TURNBULL

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

IN

EXPERIMENTAL SURGERY

DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

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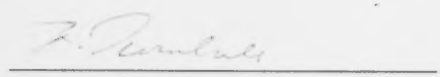

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled Hemodynamic Changes and Gut Barrier Function in Sequential Periods of Hypovolemic and Endotoxic Shock submitted by Robert G. Turnbull in partial fulfilment of the requirements for the degree of Master of Science in Experimental Surgery.

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ABSTRACT

Multisystem organ failure (MSOF) is the major cause of late death following trauma. The gut is hypothesized to be the source of bacteria and toxins which initiate and perpetuate the state of systemic inflammation that characterizes MSOF. It has also been suggested that while a single physiologic insult might not reliably cause MSOF, the addition of a delayed second stress will. This is known as the 'two-hit' theory. This study has attempted to investigate the two-hit theory by observing the response to a second stress in a subacute pig model of hemorrhagic and endotoxic shock.

Seventeen female swine (30 - 40 kg) were anaesthetized and underwent cannulation of the internal carotid artery, external jugular vein, and portal vein. An ultrasonic flow probe was placed about the craniomesenteric artery. Wounds were closed and catheters tunneled to allow the animal to recover between experimental days. Animals were assigned to Group I (n=6), Group II (n=6), or Group III (n=5). Group I underwent surgery only on Day 1, then received an infusion of endotoxin (25 mcg/kg E. coli lipopoly-saccharide) on Day 3. Group II were put into hemorrhagic shock (MAP = 40) for four hours on Day 1, then received endotoxin on Day 3. Group III animals were hemorrhaged on Day 1, and underwent anaesthesia only (as a control) on Day 3. All animals were sacrificed on Day 5 and tissues were sampled for bacterial culture.

In response to endotoxin, Group I animals displayed a typical transient hyperdynamic response followed by a distributive shock state. Group II animals failed to mount the initial hyperdynamic response, but simply fell into a shock state with sustained impairment of delivery of oxygen to the gut and resulting mucosal acidosis. Group II animals also showed a significantly higher incidence of tissue infection, bacteremia, polymicrobial infection, and infection with *Enterococcus*.

This data suggests a difference in response to a physiologic insult when an initial stressor has been previously endured. Impaired handling of a second stress could contribute to development of MSOF as proposed by the two-hit theory.

TABLE OF CONTENTS

INTRODUCTION	1
LITERATURE REVIEW	2
I. Overview of Multisystem Organ Failure	2
II. Role of Gut in Multisystem Organ Failure	4
III. Bacterial Translocation	6
A. Bacterial Overgrowth	7
B. Thermal Injury	9
C. Nutrition	11
D. Immune Modulation	14
E. Irradiation	17
F. Endotoxin	18
G. Hemorrhagic Shock	23
H. Human Studies	27
I. Attenuation	29
J. Mechanisms	31
VI. Two - Hit Theory	34
V. Summary	36
EXPERIMENTAL DESIGN	37
MATERIALS AND METHODS	39
I. Animal Preparation	39
II. Surgical Procedures	41
A. Aseptic Technique	41
B. Carotid Artery and External Jugular Vein Catheterization	41
C. Abdominal Operation	42

III. Hemorrhagic Shock 44
IV. Endotoxic Shock 45
V. Tissue Sampling 46
VI. Euthanasia 46
VII. Monitoring During Shock Periods 46
A. Hemodynamic Monitoring 47
B. Biochemical / Hematological Monitoring 49
C. Bacteriological Monitoring 54
VIII. Statistical Method 55
RESULTS 57
I. Exclusion / Dropout Criteria and Mortality 57
II. Hemodynamics 59
A. Heart Rate 60
B. Mean Arterial Pressure 63
C. Central Venous Pressure 68
D. Craniomesenteric Arterial Flow 71
E. Fraction of Inspired Oxygen 75
F. Animal Weights 76
III. Biochemistry 77
A. Arterial Partial Pressure of Oxygen 77
B. Arterial Partial Pressure of Carbon Dioxide 79
C. Arterial Hydrogen Ion Concentration 82
D. Arterial Bicarbonate Concentration 84
E. Arterial Oxygen Saturation 87
F. Portal Venous Partial Pressure of Oxygen 89
G. Portal Venous Hydrogen Ion Concentration 93
H. Portal Venous Oxygen Saturation 96

I. Hemoglobin Concentration 99
J. Content of Oxygen in Arterial Blood 104
K. Delivery of Oxygen to Gut 108
L. Content of Oxygen in Portal Venous Blood 110
M. Gradient of Oxygen Content of Arterial vs. Portal Venous Blood 114
N. Oxygen Uptake by the Gut 118
O. Oxygen Extraction Ratio of the Gut 121
P. Sigmoid Colon Mucosal Hydrogen Ion Concentration 125
Q. Serum Endotoxin Level 132
R. Serum Lactate Level 134
S. Serum Glucose Level 136
T. Serum Cortisol Level 138
IV. Bacteriology 140
A. Blood Cultures 141
B. Lymph Nodes 143
C. Solid Organs 145
DISCUSSION 149
I. Experimental Design 149
II. Swine Model 151
III. Hemodynamics 154
IV. Biochemistry 156
V. Bacteriology 161
CONCLUSIONS 163
RECOMMENDATIONS 166
BIBLIOGRAPHY 168

LIST OF FIGURES

		Page
Figure 1.	Two-Hit Theory of Multisystem Organ Failure	35
Figure 2.	Experimental Time Schedule	38
Figure 3.	Heart Rate for T=4 to T=8 (Day 1) - Hemorrhage	60
Figure 4.	Heart Rate for T=48 to T=52 (Day 3) - Endotoxin Infusion	62
Figure 5.	Mean Arterial Pressure for T=4 to T=8 (Day 1) - Hemorrhage	64
Figure 6.	Mean Arterial Pressure for T=48 to T=52 (Day 3) - Endotoxin Infusion	66
Figure 7.	Central Venous Pressure for T=49 to T=52 (Day 3) - Endotoxin Infusion	70
Figure 8.	Craniomesenteric Arterial Flow of Four Group II and Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	72
Figure 9.	Craniomesenteric Arterial Flow for T=48 to T=52 (Day 3) - Endotoxin Infusion	73
Figure 10.	Partial Pressure of Oxygen in Portal Venous Blood for T=4 to T=8 (Day 1) - Hemorrhage	90
Figure 11.	Partial Pressure of Oxygen in Portal Venous Blood for T=48 to T=52 (Day 3) - Endotoxin Infusion	91
Figure 12.	Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood for T=4 to T=8 (Day 1) - Hemorrhage	93
Figure 13.	Portal Venous Hydrogen Ion Concentration for T=48 to T=52 (Day 3) - Endotoxin Infusion	95
Figure 14.	Oxygen Saturation (percent) of Portal Venous Blood for T=4 to T=8 - Hemorrhage	97
Figure 15.	Hemoglobin Concentration in Arterial Blood for T=4 to T=8 (Day 1) - Hemorrhage	100
Figure 16.	Hemoglobin Concentration in Arterial Blood for T=48 to T=52 (Day 3) - Endotoxin Infusion	102

Figure 17.	Oxygen Content in Arterial Blood for T=4 to T=8 (Day 1) - Hemorrhage	104
Figure 18.	Content of Oxygen in Arterial Blood for T=48 to T=52 (Day 3) - Endotoxin Infusion	106
Figure 19.	Gut Oxygen Delivery for T=48 to T=52 (Day 3) - Endotoxin Infusion	108
Figure 20.	Oxygen Content of Portal Venous Blood for T=4 to T=8 (Day 1) - Hemorrhage	111
Figure 21.	Oxygen Content of Portal Venous Blood for T=48 to T=52 (Day 3) - Endotoxin Infusion	113
Figure 22.	Arterial-Portal Oxygen Content Gradient for T=4 to T=8 (Day 1) - Hemorrhage	115
Figure 23.	Arterial-Portal Oxygen Content Gradient for T=48 to T=52 (Day 3) - Endotoxin Infusion	117
Figure 24.	Gut Oxygen Uptake for T=48 to T=52 (Day 3) - Endotoxin Infusion	119
Figure 25.	Gut Oxygen Extraction Ratio for T=4 to T=8 (Day 3) - Hemorrhage	122
Figure 26.	Gut Oxygen Extraction Ratio for T=48 to T=52 (Day 3) - Endotoxin Infusion	124
Figure 27.	Sigmoid Colon Mucosal Hydrogen Ion Concentration for T=4 to T=8 (Day 1) - Hemorrhage	126
Figure 28.	Sigmoid Colon Mucosal Hydrogen Ion Concentration for T=48 to T=52 (Day 3) - Endotoxin Infusion	129
Figure 29.	Serum Endotoxin Level for T=48 to T=52 (Day 3) - Endotoxin Infusion	132
Figure 30.	Serum Lactate Level for T=48 to T=52 (Day 3) - Endotoxin Infusion	134
Figure 31.	Serum Glucose Level for T=48 to T=52 (Day 3) - Endotoxin Infusion	136
Figure 32.	Serum Cortisol Level for T=48 to T=52 (Day 3) - Endotoxin Infusion	138

LIST OF TABLES

		Page
Table 1.	Clinical Stages of Multisystem Organ Failure	3
Table 2.	Hemodynamic Parameters and Time Schedule of Measurements - Day 1	47
Table 3.	Hemodynamic Parameters and Time Schedule of Measurements - Day 3	48
Table 4.	Biochemical / Hematological Monitoring and Time Schedule of Measurements	49
Table 5.	Heart Rate (bpm) for Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	60
Table 6.	Heart Rate (bpm) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	61
Table 7.	Heart Rate (bpm) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	61
Table 8.	Heart Rate (bpm) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	62
Table 9.	Heart Rate (bpm) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	63
Table 10.	Heart Rate (bpm) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	63
Table 11.	Mean Arterial Pressure (mmHg) of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	64
Table 12.	Mean Arterial Pressure (mmHg) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	65
Table 13.	Mean Arterial Pressure (mmHg) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	65
Table 14.	Mean Arterial Pressure (mmHg) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	66
Table 15.	Mean Arterial Pressure (mmHg) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	67

Table 16.	Mean Arterial Pressure (mmHg) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	67
Table 17.	Central Venous Pressure (mmHg) of Group I Animals for T=4 to T=8 (Day 1) -Hemorrhage	68
Table 18.	Central Venous Pressure (mmHg) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	68
Table 19.	Central Venous Pressure (mmHg) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	69
Table 20.	Central Venous Pressure (mmHg) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	70
Table 21.	Central Venous Pressure (mmHg) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	71
Table 22.	Central Venous Pressure (mmHg) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	71
Table 23.	Craniomesenteric Arterial Flow (percent of baseline) of Group II and Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	72
Table 24.	Craniomesenteric Arterial Flow (percent of baseline) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	74
Table 25.	Craniomesenteric Arterial Flow (percent of baseline) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	74
Table 26.	Craniomesenteric Arterial Flow (percent of baseline) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	74
Table 27.	Fraction of Inspired Oxygen (percent) for Group I Animals (T=48 to T=52)	75
Table 28.	Fraction of Inspired Oxygen (percent) for Group II Animals (T=48 to T=52)	75
Table 29.	Fraction of Inspired Oxygen (percent) for Group III Animals (T=48 to T=52)	76
Table 30.	Weights of Experimental Animals (in kilograms)	76
Table 31.	Partial Pressure of Oxygen (mmHg) in Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	77

Table 32.	Partial Pressure of Oxygen (mmHg) in Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	78
Table 33.	Partial Pressure of Oxygen (mmHg) in Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	78
Table 34.	Partial Pressure of Oxygen (mmHg) of Arterial Blood in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	78
Table 35.	Partial Pressure of Oxygen (mmHg) of Arterial Blood in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	79
Table 36.	Partial Pressure of Oxygen (mmHg) in Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	79
Table 37.	Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	80
Table 38.	Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	80
Table 39.	Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	81
Table 40.	Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	81
Table 41.	Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	81
Table 42.	Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	82
Table 43.	Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	82
Table 44.	Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	83
Table 45.	Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	83
Table 46.	Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	83

Table 47.	Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	84
Table 48.	Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	84
Table 49.	Arterial Bicarbonate (nmol/l) of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	85
Table 50.	Arterial Bicarbonate (nmol/l) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	85
Table 51.	Arterial Bicarbonate (nmol/l) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	85
Table 52.	Arterial Bicarbonate (nmol/l) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	86
Table 53.	Arterial Bicarbonate (nmol/l) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	86
Table 54.	Arterial Bicarbonate (nmol/l) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	87
Table 55.	Oxygen Saturation (percent) of Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	87
Table 56.	Oxygen Saturation (percent) of Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	88
Table 57.	Oxygen Saturation (percent) of Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	88
Table 58.	Oxygen Saturation (percent) of Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	88
Table 59.	Oxygen Saturation (percent) of Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	89
Table 60.	Oxygen Saturation (percent) of Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	89
Table 61.	Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	90
Table 62.	Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	91

Table 63.	Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	92
Table 64.	Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	92
Table 65.	Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	92
Table 66.	Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	93
Table 67.	Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	94
Table 68.	Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	94
Table 69.	Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	95
Table 70.	Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	96
Table 71.	Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	96
Table 72.	Oxygen Saturation (percent) of Portal Venous Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	97
Table 73.	Oxygen Saturation (percent) of Portal Venous Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	97
Table 74.	Oxygen Saturation (percent) of Portal Venous Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	98
Table 75.	Oxygen Saturation (percent) of Portal Venous Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	98
Table 76.	Oxygen Saturation (percent) of Portal Venous Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	99

Table 77.	Oxygen Saturation (percent) of Portal Venous Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	99
Table 78.	Hemoglobin Concentration (g/dl) in Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	100
Table 79.	Hemoglobin Concentration (g/dl) in Arterial Blood of Group II for T=4 to T=8 (Day 1) - Hemorrhage	101
Table 80.	Hemoglobin Concentration (g/dl) in Arterial Blood of Group III for T=4 to T=8 (Day 1) - Hemorrhage	101
Table 81.	Hemoglobin Concentration (g/dl) in Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	103
Table 82.	Hemoglobin Concentration (g/dl) in Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	103
Table 83.	Hemoglobin Concentration (g/dl) in Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	103
Table 84.	Oxygen Content (mlO_2/dl) of Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	105
Table 85.	Oxygen Content (mlO_2/dl) of Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	105
Table 86.	Oxygen Content (mlO_2/dl) of Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	105
Table 87.	Oxygen Content (mlO_2/dl) of Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	107
Table 88.	Oxygen Content (mlO_2/dl) of Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	107
Table 89.	Oxygen Content (mlO_2/dl) of Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	107
Table 90.	Gut Oxygen Delivery (mlO2/min) for T=48 to T=52 (Day 3) - Endotoxin Infusion	109
Table 91.	Gut Oxygen Delivery (percent of baseline) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	109

Table 92.	Gut Oxygen Delivery (percent of baseline) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	110
Table 93.	Gut Oxygen Delivery (percent of baseline) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	110
Table 94.	Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	111
Table 95.	Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	112
Table 96.	Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	112
Table 97.	Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	113
Table 98.	Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	114
Table 99.	Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	114
Table 100.	Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	115
Table 101.	Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	116
Table 102.	Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	116
Table 103.	Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	117
Table 104.	Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	118
Table 105.	Arterial - Portal Oxygen Content Gradient of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	118
Table 106.	Gut Oxygen Uptake (mlO2/min) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	120

Table 107.	Gut Oxygen Uptake (percent of baseline) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	120
Table 108.	Gut Oxygen Uptake (percent of baseline) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	121
Table 109.	Gut Oxygen Uptake (percent of baseline) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	121
Table 110.	Gut Oxygen Extraction Ratio in Group I Animals for T=4 to T=8 (Day 3) - Hemorrhage	122
Table 111.	Gut Oxygen Extraction Ratio in Group II Animals for T=4 to T=8 (Day 3) - Hemorrhage	123
Table 112.	Gut Oxygen Extraction Ratio in Group III Animals for T=4 to T=8 (Day 3) - Hemorrhage	123
Table 113.	Gut Oxygen Extraction Ratio in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	124
Table 114.	Gut Oxygen Extraction Ratio in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	125
Table 115.	Gut Oxygen Extraction Ratio in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	125
Table 116.	Sigmoid Colon Mucosal Hydrogen Ion Concentration (nmol/l) for T=4 to T=8 (Day 1) - Hemorrhage	127
Table 117.	Sigmoid Colon Mucosal Hydrogen Ion Concentration (as percent of baseline) in Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage	127
Table 118.	Sigmoid Colon Mucosal Hydrogen Ion Concentration (as percent of baseline) in Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage	128
Table 119.	Sigmoid Colon Mucosal Hydrogen Ion Concentration (as percent of baseline) in Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage	128
Table 120.	Sigmoid Colon Mucosal Hydrogen Ion Concentration (nmol/l) for T=48 to T=52 (Day 3) - Endotoxin Infusion	130

Table 121.	Sigmoid Colon Mucosal Hydrogen Ion Concentration (percent of baseline) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	130
Table 122.	Sigmoid Colon Mucosal Hydrogen Ion Concentration (percent of baseline) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	131
Table 123.	Sigmoid Colon Mucosal Hydrogen Ion Concentration (percent of baseline) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	131
Table 124.	Serum Endotoxin Level (Endotoxin Units) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	133
Table 125.	Serum Endotoxin Level (Endotoxin Units) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	133
Table 126.	Serum Endotoxin Level (Endotoxin Units) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	133
Table 127.	Serum Lactate Level (mg/dl) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	135
Table 128.	Serum Lactate Level (mg/dl) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	135
Table 129.	Serum Lactate Level (mg/dl) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	135
Table 130.	Serum Glucose Level (mg/dl) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	137
Table 131.	Serum Glucose Level (mg/dl) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	137
Table 132.	Serum Glucose Level (mg/dl) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	137
Table 133.	Serum Cortisol Level (nmol/l) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	139
Table 134.	Serum Cortisol Level (nmol/l) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	139
Table 135.	Serum Cortisol Level (nmol/l) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion	139

Table 136.	Bacteria Considered Common Enteric Organisms	140
Table 137.	Bacteria Considered Contaminants	141
Table 138.	Organisms Isolated from Systemic Blood of Group I Animals	141
Table 139.	Organisms Isolated from Systemic Blood of Group II Animals	142
Table 140.	Organisms Isolated from Systemic Blood of Group III Animals	142
Table 141.	Summary of Arterial Blood Cultures	142
Table 142.	Organisms Isolated From Lymph Node Cultures (taken at T=96) of Group I Animals	143
Table 143.	Organisms Isolated From Lymph Node Cultures (taken at T=96) of Group II Animals	144
Table 144.	Organisms Isolated From Lymph Node Cultures (taken at T=96) of Group III Animals	144
Table 145.	Summary of Lymph Node Tissue Cultures	145
Table 146.	Organisms Isolated from Tissue Cultures (taken at T=96) of Group I Animals	146
Table 147.	Organisms Isolated from Tissue Cultures (taken at T=96) of Group II Animals	146
Table 148.	Organisms Isolated from Tissue Cultures of Group III Animals	147
Table 149.	Summary of Solid Organ Tissue Cultures	147
Table 150.	Incidence of Positive Tissue Cultures by Organ	147
Table 151.	Summary of Culture Specimens Positive for Polymicrobial Infection (> 1 Pathogen)	148

List of Abbreviations

bpm	beats per minute
$C_{a\text{-}p}O_2$	Arterial - portal venous oxygen content gradient
CAF	Craniomesenteric Arterial Flow
C_aO_2	Content of oxygen in arterial blood
cm	centimeter(s)
C_pO_2	Content of oxygen in portal blood
CVP	Central Venous Pressure
dl	decilitre(s)
$DO2_g$	Rate of delivery of oxygen to the gut
E. coli	Escherichia coli
F_iO_2	Fraction of inspired oxygen
g	gram
GALT	Gut-Associated Lymphoid Tissue
GI	Gastrointestinal
$[H+]_a$	Hydrogen ion concentration in arterial blood
$[H+]_p$	Hydrogen ion concentration in portal blood
HCO_{3a}	Bicarbonate concentration in arterial blood
HCO_{3p}	Bicarbonate concentration in portal blood
Hgb	Hemoglobin concentration
hr	hour(s)
HR	Heart Rate
IgA	Immunoglobulin A
Il-2	Interleukin-2
IM	Intramuscular
IV	Intravenous
kg	kilogram(s)
l	litre(s)
LDH	Lactate Dehydrogenase
MAP	Mean Arterial Pressure
mcg	microgram(s)
min	minute
ml	millilitre(s)
MLN	Mesenteric Lymph Node
mm	millimeter(s)
mmHg	millimeters of mercury
mmol	millimole
MSOF	Multisystem Organ Failure
NAD	Nicotinamide Adenine Dinucleotide

nmol	nanomole
O_2	oxygen
^oC	degrees Celcius
P_aCO_2	Partial pressure of carbon dioxide in arterial blood
PAF	Platelet Activating Factor
P_aO_2	Partial pressure of oxygen in arterial blood
pHi	Intestinal mucosa pH
P_pCO_2	Partial pressure of carbon dioxide in portal blood
P_pO_2	Partial pressure of oxygen in portal blood
S.E.M.	Standard Error of the Mean
S_aO_2	Oxygen saturation of arterial blood
SPF	Specific Pathogen Free
S_pO_2	Oxygen saturation of portal blood
Std.Dev.	Standard Deviation
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
VO_{2g}	Rate of uptake of oxygen by the gut
vs.	versus

INTRODUCTION

The history of medicine has been one of trials and tribulations brought on by the need to overcome obstacles. Often, as we attain the ability to treat one condition, another reveals itself in patients who would have previously succumbed to that which has just been defeated. In addition, it may be discovered that the newfound clinical intervention is itself, fraught with complications, sometimes more malevolent than the original illness. Such has long been the case in the care of the critically ill and injured patient. The treatment of infection, followed by renal failure, followed by adult respiratory distress syndrome, followed by multisystem organ failure have all been examples of this.

The most recent link in this chain, multisystem organ failure, is proving to be a formidable adversary. It is a global condition arising from a wide variety of physiologic insults and carrying a high rate of morbidity and mortality. The complex. interrelationships between inciters, mediators and target organs has become a very active topic of research over the past twenty years and has incorporated input from the disciplines of molecular biology, microbiology, and surgery. Much of this work has suggested that the gut plays a pivotal role as both an inciter and as a target organ in this condition[1]. It has also been suggested that a combination of physiologic injuries is more likely to cause organ failure than a single insult[2].

It is the purpose of this thesis to further define the role of the gut and the role of combined stressful events in a model of a critically ill patient. Before addressing this, however, a review of the pertinent literature is necessary.

I. OVERVIEW OF MULTISYSTEM ORGAN FAILURE

Over the past several decades, major advances have been made in the support of traumatized and critically ill patients. Infection in the 1940s, renal failure in the 1950s and respiratory failure in the 1960s were common causes of death in this patient population. With advances in overcoming these obstacles, the relatively new syndrome of Multisystem Organ Failure (MSOF) has come into light as the major cause of mortality in patients surviving the initial acute phase of their injury.

The variety of disease states capable of causing MSOF is vast. Most commonly, it results from shock and infection[3], but conditions such as pancreatitis, malnutrition, burns, devitalized tissue, and immune suppression may also be contributing factors. Virtually any inflammatory, ischemic or metabolic stress may be implicated. Patients undergoing emergency operations have an estimated risk of 7-22% for developing MSOF[1]. In those undergoing surgery for intra-abdominal sepsis, the risk is 30-50%[1]. Mortality has been estimated from 30-100% but is generally felt to be in excess of 60% overall[4] and has not changed appreciably over the past 20 years since early descriptions of the syndrome. Mortality rate appears to be directly proportional to the number of organ systems clinically involved, progressing from 30% with one system, to 100% with four organ system failures[5].

This condition is characterized by a hyperdynamic, hypermetabolic state identical to that seen in sepsis. It is accompanied by a systemic inflammatory response which seems to be modulated by a cascade of soluble protein and lipid mediators which furthers the resemblance to sepsis[4]. These mediators are, for the most part, endogenously produced,

thus it must be borne in mind that, in this condition, the host is not an innocent bystander. From a clinical perspective, the syndrome follows an orderly pattern of sequential organ system dysfunction which first involves the lungs, followed by liver, intestines, then kidneys, and late in the course, cardiovascular and hematopoietic failure[3]. The clinical signs and symptoms of the progression of this syndrome, were described by C.J. Carrico at a Panel Discussion of the Surgical Infection Society in 1985[1]:

Table 1. Clinical Stages of the Multisystem Organ Failure Syndrome

	Stage I	Stage II	Stage III	Stage IV
General Appearance	No obvious signs	"III", Metastable	Obviously unstable	Terminal illness
Cardiovascular Function	Increased volume requirements	Hyperdynamic, volume dependent	Shock, decreased cardiac output, edema	Inotropes, volume "overload"
Respiratory Function	Mild respiratory alkalosis	tachypnea, hypocapnea, hypoxia	Severe hypoxia	Hypercapnea, barotrauma
Renal Function	Limited responsiveness	Fixed output, minimal azotemia	Azotemia	Oliguria
Metabolism	Increased insulin requirements	Severe catabolism	Metabolic acidosis, hyperglycemia	Severe acidosis, increased oxygen consumption
Hepatic Function	?	Chemical jaundice	Clinical jaundice	Encephalopathy
Hematology	?	Decreased platelet count, increased or decreased WBC	Coagulopathy	Immature cells, coagulopathy
Central Nervous System	Confusion	Variable	Some response	Coma

The symptoms of increased cardiac output, decreased vascular resistance, impaired perfusion, fever, and leukocytosis were noted to progress in a predictable manner with a downhill course. In the late 1970s, septic shock had become an uncommon manifestation of systemic infection only to be superseded by MSOF. Many of these patients were found to harbor occult infections thus an era of extensive use of empiric antibiotic therapy and "blind" laparotomy in search of intra-abdominal abscess was initiated[1,5,6]. Eventually, however, it was noticed that a significant group of patients had persistently negative blood

cultures and laparotomies despite the classic findings of fever, leukocytosis and remote organ dysfunction with progressive deterioration[7,8]. Because MSOF is a systemic disease at the cellular level, it's treatment must be founded in molecular and cellular biology with an understanding of the complex interactions of the mediator molecules, their sources and their target organs. The need to understand the etiology of this syndrome has prompted an enormous amount of research in the field of trauma and critical care. Despite these efforts, the basic pathophysiology of this syndrome remains to be fully elucidated.

II. ROLE OF GUT IN MULTISYSTEM ORGAN FAILURE

During critical illness, a number of factors play a role in the development of MSOF but the exact mechanism remains controversial. At its most basic level, it is a cellular disease mediated by protein and lipid molecules which interact with each other and their target organs in ways which are only beginning to be understood. The "gut hypothesis"[3] suggests that intestinally derived bacteria or bacterial cell wall lipopolysaccharides (endotoxins) serve as trigger to initiate, perpetuate, or exacerbate the septic state and thereby promote the development of MSOF. Bacteria and endotoxin efficiently induce cytokine secretion by resident tissue macrophages, promote a proinflammatory endothelial cell phenotype, stimulate neutrophil protease and oxidant production, and activate humoral protein cascades (complement, coagulation). Once initiated, these processes further impair the gut's ability to provide a barrier from intraluminal bacteria and endotoxin and thus a self-perpetuating cycle is initiated[9]. The phenomenon of this loss of gut mucosal barrier function is referred to as bacterial translocation. This theory suggests

why many patients developing MSOF do not develop bacteremia or do so in the absence of an identifiable source of infection[10]. The fact that antibiotics are not very effective in halting this process suggests that the absorption of endotoxin, or endotoxin from killed bacteria, may be more important than the viable bacteria[11].

The mucosa of the gastrointestinal (GI) tract serves as a complex barrier between its infectious and toxic intraluminal contents and the internal milieu of the organism, while at the same time serving as a route for the absorption of nutrients. This barrier is comprised of a physical force including secreted mucus, epithelial cells, tight intracellular junctions, and indigenous microorganisms. As well, there are immunologic barriers which include gut associated lymphoid tissue (GALT), IgA antibodies and local cell-mediated immune responses[12]. This barrier function can be lost in critical illness due to impaired oxygen delivery, bacterial overgrowth, immune suppression, inadequate nutrition, and/or cytokine activity[1]. In many cases, clinical therapeutic interventions contribute to these changes and further the damage to the gut barrier. It's effectiveness varies with age as it has been shown in animal models that neonates are more susceptible to the movement of bacteria from the intestinal lumen to the liver[13].

While there is increasing agreement that bacterial translocation from the intestine occurs in the course of traumatic shock, there are a spectrum of opinions as to the significance of this phenomenon, ranging from the statement that 'the gut is the motor of multiorgan failure'[1], to the opinion of others that bacteria translocation is an epiphenomena that occurs in traumatic shock, but has little bearing on the outcome[14]. The truth will require further investigation.

III. BACTERIAL TRANSLOCATION

The most frequently quoted definition of bacterial translocation is one given by Berg et al[15] in 1979 describing it as "the passage of viable bacteria from the gastrointestinal tract through the epithelial mucosa into the lamina propria, then on to the mesenteric lymph nodes and possibly other organs". A revised definition put forth by Alexander et al[16] in 1990 also includes mention of non-viable bacteria and endotoxin and is therefore more complete, stating that "bacterial translocation is the passage of viable and nonviable microbes, as well as microbial components (such as endotoxin), across an anatomically intact intestinal barrier". Although these are the modern working definitions, the concept of the passage of enteric toxins beyond the lumen of the gut has been postulated for almost 100 years[17]. Generally, the phenomenon is demonstrated by the culture of enteric microorganisms from normally sterile tissues such as mesenteric lymph nodes (MLNs), liver, spleen, kidney, lung or blood. Other techniques utilize radiolabelled bacteria[18], inert particles[19] or macromolecules such as radiolabelled chromium EDTA[20], lactulose[21] or polethylene glycol[22]. It should be emphasized that translocation refers to indigenous bacteria, and not to those bacteria which are externally acquired or nonindigenous.

A number of diverse stressors can cause translocation, including something as mild as simple surgical intestinal handling[23,24]. Other causes include direct mucosal injury from ricinoleic acid[25], methotrexate[26] or radiation[27]. The more commonly studied precipitants are those which are generally implicated in the pathogenesis of MSOF and will be reviewed more extensively herein. These include thermal injury, endotoxin and hemorrhagic shock. Bacterial overgrowth, cessation of enteric feeding, and immune suppression commonly occur in the critically ill patient in the intensive care unit and are

also thought to be involved in loss of gut mucosal barrier function. Bacterial translocation is of itself considered to be a predisposing factor for systemic infections[14,28], postinjury hypermetabolism[29], MSOF[1], and clinical sepsis in the absence of defined focus of infection[10].

A. Bacterial Overgrowth

An orderly acquisition of intestinal microbial flora develops in mammals after birth and a precise balance of these organisms is required for maintenance of normal digestive function. Bacterial populations affect the susceptibility of the mucosa to colonization and invasion by pathogenic bacteria thus alterations have the potential to result in a disease state[12]. Pseudomembranous colitis and salmonella dysentery are examples of this.

In one of the earlier studies of bacterial translocation, Berg et al[15] found that viable enteric bacteria could be isolated from the mesenteric lymph nodes of gnotobiotic mice after their GI tracts had been inoculated with the cecal microflora of specific-pathogen-free (SPF) mice. Also, monoassociation of the GI tracts of the gnotobiotic mice with various individual indigenous strains of bacteria resulted in translocation of viable organisms into MLNs. In another study by Berg[30], gnotobiotic mice were monoassociated with a specific strain of *Escherichia coli* (*E. coli*) and translocation to MLNs occurred. These mice were then intragastrically inoculated with the cecal contents of SPF mice resulting in a significant quantitative reduction in the incidence of translocation to lymph nodes. The importance of viability of the inoculated bacteria was confirmed when this reduction of translocation was not seen after inoculation with heated, formalin treated, or filtered SPF mouse cecal contents. The same investigator has shown a

direct relationship between the numbers of a particular bacterial strain populating the cecum of diassociated or triassociated mice and the numbers of viable bacteria of this strain translocating to the MLN[31] indicating the importance of the relative proportions of enteric bacteria. To clarify this further, experiments were carried out in which SPF mice were treated with a course of either oral penicillin, metronidazole or clindamycin[32]. Each resulted in alterations of cecal bacterial populations with overgrowth and translocation of enteric bacilli . A more clinically relevant perspective of this phenomenon was presented when SPF mice, receiving a 40% body surface area (BSA) burn, developed bacterial translocation to MLN but were shown to have bacteria in liver and spleen, as well as MLN, after burn plus oral penicillin or E. coli monoassociation[33]. A similar study[34] found the same results from the additive effects of an immune suppressant drug and an oral antibiotic. The impact of antibiotic decontamination of the GI tract on outcome for burn patients and those on immune suppressants remains an issue of controversy.

While anaerobes are the most populous of intestinal flora, they are almost never found to translocate[15]. To investigate their role in the phenomenon of translocation, Wells et al[35] selectively decontaminated the GI tracts of mice orally inoculated with antibiotic-resistant *E. coli*. Those in which anaerobe populations were eliminated demonstrated markedly higher counts of *E. coli* (and other indigenous bacteria) in MLNs suggesting that anaerobes play a key role in confining indigenous bacteria to the gut.

Deitch et al[36] examined the effect of common bile duct ligation on bacterial translocation in mice. They found that obstructive jaundice was associated with a higher incidence of translocation to MLN than sham-operation and that ligated animals showed higher (not statistically significant) cecal populations of gram negative enteric bacilli. Other clinically relevant studies by the same authors reviewed the effects of intestinal obstruction on gut barrier function. The MLNs of human subjects undergoing laparotomy for intestinal obstruction were sampled and cultured showing the presence of enteric flora

which was not seen in nodes from patients undergoing laparotomy for other reasons[37]. Mice in which the intestine was experimentally ligated[38] demonstrated translocation to MLNs within 6 hours of operation and systemic sepsis within 24 hours despite bowel integrity. Composition of cecal flora changed and total populations increased dramatically after ligation of bowel (either proximal or distal to cecum). Interestingly, the histology of the mucosa proximal to ligation was normal in gnotobiotic mice while that of SPF mice showed severe mucosal edema. Mucosal damage is not seen in bacterial overgrowth without intestinal obstruction[39]. This suggests that luminal bacteria and/or their products play a role in the pathogenesis of intestinal mucosal injury after intestinal obstruction.

B. Thermal Injury

Deitch et al., Herndon et al., and Shires et al., have developed excellent, reproducible models of bacterial translocation following burn injury in rodents, sheep, and swine. They have shown that translocation of gut flora to mesenteric lymph nodes readily occurs after burns and with the added insults of intestinal bacterial overgrowth[33], endotoxin[40], exogenous corticosterone[41], as well as some other alterations of normal physiology, the infection may be spread beyond the nodes to organs such as liver and spleen.

In burn injury, neutrophil chemotaxis, phagocytosis and bacterial killing are impaired, and T-suppressor cell population is elevated[42]. Evidence of cell-mediated immune suppression includes skin test anergy, depression of lymphocyte proliferation in response to mitogens and allogeneic cells, decreased activity in natural killer (NK) and antibody-dependent cellular cytotoxicity assays, and increased allograft rejection times.

Also, serum immunoglobulin (Ig) levels have been noted to fall after burn injury[43]. The mechanisms by which these phenomena occur is doubtless extremely complex and investigators are only beginning to isolate some of the low molecular weight mediators involved, such as prostaglandin E, prostaglandin A, suppressor active peptide, interferon, endotoxin, corticosteroids and histamine[44,45].

Burns have also been reported to impair mucosal barrier function by reducing mesenteric blood flow[46,47] (thromboxane[48],vasopressin and angiotensin implicated[49]) resulting in ischemia and mucosal damage[50,51], reducing mucosal mass and mucosal DNA synthesis[52,53,54,55], and increasing mucosal permeability[56,57]. Thus bacteria are able to reach the MLNs and, possibly initiate a septic response when their survival is enhanced by burn-initiated immune suppression or another stressor such as burn wound infection. If these lymph nodes are able to clear themselves[58,59], or are surgically removed[60], disseminated infection does not occur.

Alternatively, intraluminal bacterial endotoxin may be systemically absorbed when mucosal barrier function is lost after burn injury thus initiating a cascade of reactions promoting disseminated infection (vide infra). Other theories for the mechanism of intestinal bacteria causing septic consequences of major thermal injury include transmural migration into peritoneal fluid or absorption of bacteria into the lamina propria and then on to the liver and systemic tissues[60]. These possibilities, however, are not favored by other investigators[61].

C. Nutrition

The role of enteral feeding in the critically ill patient has steadily become more prominent in the medical literature. A review by Wilmore et al[62] in 1988 discussed how the 'rested' gut may allow the efflux of endotoxin and bacteria from the gut lumen because many nutrients essential to normal enterocyte growth are lacking in parenteral nutrition. The presence of food itself in the gut stimulates mucosal cell turnover by desquamating villus tips, providing nutrients, and causing production of mucosa-trophic hormones[62]. The gut mucosal barrier is really comprised of two elements: the physical barrier of mucus, tight cellular junctions and indigenous bacteria, and the gut-associated lymphoid tissue (GALT) which consists of Peyer's patches, lymphoid follicles, lamina propria lymphocytes, and MLNs[63]. The importance of maintaining this barrier's function through proper enteral nutrition has been investigated experimentally.

A study by Alverdy et al[64] examined bacterial translocation in parenterally fed rats as opposed to others fed total parenteral nutrition (TPN) solution orally, and a group receiving normal solid food. After 2 weeks, parenterally-fed rats showed 66% culture-positive MLNs while 33% of those receiving enteral TPN solution and 0% of those eating normal feed had bacteria in MLNs. Cecal bacterial counts were also elevated in animals receiving TPN solution, regardless of the route of administration. IgA levels in bile were also noted to be diminished in parenterally-fed animals. The effects of protein malnutrition on bacterial translocation have been studied by Deitch et al in a series of experiments[39,65,66]. They have shown that translocation does not occur in mice starved for 72 hours, or protein malnourished for 21 days. However, mice receiving an endotoxin challenge after the period of malnutrition developed significantly greater frequency and magnitude of translocation of bacteria to MLNs as well as showing histologic evidence of

mucosal damage without any difference in cecal bacterial populations. Surprisingly, the addition of a burn stress or E.coli monoassociation following protein malnutrition did not enhance bacterial translocation although the cecal population of gram negative bacilli did increase. Further experimentation by this group[67] reviewed the effect of fiber on translocation in rats thus expanding on the work by Alverdy et al. Rats were fed either oral or intravenous TPN solution in addition to cellulose powder. The addition of cellulose significantly decreased the incidence of bacterial translocation to MLNs in both groups despite having no effect on loss of mucosal mass or intraluminal bacterial overgrowth. This supports the importance of residue-containing enteral nutrition in the critically ill patient.

It has been well-established that the primary respiratory fuel of the enterocytes is a balance of circulating and intraluminal glutamine[68,69,70,71]. Windemueller and Spaeth[72] have extensively researched glutamine metabolism in rats and have found that 20-30% of plasma glutamine is extracted with each splanchnic circulation. Glutamine, itself a non-essential amino acid, serves as the nitrogen donor for purine and pyrimidine biosynthesis and thus may support crypt cell turnover end enhance healing of injured epithelium. It may also enter the tricarboxylic acid cycle (at the level of alpha-ketoglutarate) to produce energy in the form of adenosine triphosphate (ATP). The exact mechanism by which glutamine supports gut barrier function remains somewhat unclear and is likely multifactorial. In a series of experiments on rats, Fox et al[26] have shown a reduction of the severity of methotrexate-induced enterocolitis by supplementing diet with glutamine which has the effect of increasing and preserving mucosal cellularity in the small bowel. Using this same model, they have shown reduced mortality, decreased enteric bacteremia, and reduced endotoxin translocation in glutamine-supplemented animals[73]. The same experimenters have also demonstrated stimulation of colon mucosal growth by infusion of intracolonic butyrate[74,75] (a short-chain fatty acid) which serves as a principle fuel for

colonic enterocytes[76]. The lymphocytes of the GALT have similarly been shown to require glutamine for optimal function[77].

After a metabolic stress, accelerated skeletal muscle proteolysis and redistribution of amino acids such as glutamine from skeletal muscle to visceral organs occurs. In recent years, Plumley and Souba[78] have demonstrated that the lung is also a source of glutamine during the hyperdynamic phase of sepsis. Despite this increased mobilization, the circulating concentrations of glutamine are quickly diminished as it is rapidly consumed by the enterocytes[79]. The gut, however, is not simply a passive consumer of glutamine for energy, but rather, it plays an important regulatory role in processing nitrogen and carbon from other tissues into precursors (ammonia, alanine, citrulline) for hepatic ureagenesis and gluconeognesis[80]. This response is apparently mediated by the pituitary-adrenal axis as glutamine uptake by the gut has been shown to increase after exogenous glucocorticoid administration[81,82] . Repletion of glutamine stores with exogenous glutamine may not only promote "bowel rescue" but also may help maintain blood and tissue concentrations. Thus, although glutamine may have direct effects on the gut mucosa, it supports enterocyte metabolism not only via the luminal route but also via the circulating route by raising blood glutamine levels[83]. Enterocytes of the colon also utilize butyrate and keto acids as fuels[62]. These are formed respectively by fermentation of fiber by gut flora and by ketogenesis in the absence of high circulating glucose levels. Thus the use of antibiotics, gut rest, and parenteral nutrition (which does not contain glutamine) containing glucose effectively starves the gut resulting in loss of architecture, permeability barrier function and immune barrier function. If glutamine supplementation is added to TPN, preservation of small bowel mucosal architecture and prevention of bacterial translocation is facilitated[84,85,86].

D. Immune Modulation

In 1980, Berg and Owens[87] suspected that T-cell immunity would play a key role in preventing the translocation of indigenous bacteria from the gut to normally sterile organs. They studied athymic (nu/nu) mice fed a conventional diet and found a significantly higher incidence of enteric bacteria in the liver, kidney and spleen than in the nu/+ counterparts (50% vs. 5.2%). Transplantation of thymic tissue into newborn nu/nu mice provided them with sufficient immunity to bring about a reduction in incidence of translocation to parenchymal organs from 50% to 7.8%.

It has been established that after a burn injury in rats, bacteria translocate to the MLNs and, as recovery progresses, these bacteria are cleared by normal immunologic function[54,88]. The role of the glucocorticoid corticosterone in this phenomenon was studied by Jones and Shires[41,59] by attenuating the normal post-injury glucocorticoid elevation with cyclosporine. This was compared with normal and corticosterone-supplemented rodents and it was demonstrated that fewer organisms were present in MLNs after burn injury in cyclosporine-treated and normal animals than in those in which supplemental corticosterone was administered. This phenomenon was not demonstrated in other parenchymal organs sampled. Also, elevated corticosterone levels were associated with diminished lymphocyte cell populations in blood and lymph nodes while lowered corticosterone levels (from cyclosporine) were associated with higher lymphocyte numbers. These findings suggest a role for elevated glucocorticoid levels in the alteration of regional immunity after injury. Subsequently, improved survival of bacteria in mesenteric lymph nodes may occur. A confounding factor in these studies is the intrinsic ability of cyclosporine to cause bacterial translocation which was suggested by earlier studies[89] but refuted by control results in this experiment. Another study using

dexamethasone in non-traumatized rats[90] demonstrated that secretory IgA was reduced in steroid-treated animals and that mucosal adherence of bacteria and bacterial translocation to MLNs were significantly higher after steroid. This same reduction in mucosal IgA has been noted after total parenteral nutrition[64], and after burn injury[91].

With an increasing transplant population and the rising use of immune suppressive chemotherapy, the effect of these drugs on mucosal barrier function merits further study. In 1983, Berg et al[89] found that injection of an immune suppressive agent to mice resulted in translocation of enteric pathogens to the spleen, liver, kidney, and mesenteric lymph nodes. Agents used included cyclophosphamide, methotrexate, fluorouracil, prednisone, and cytarabine. In 1988[34], this effect was combined with the bacterial overgrowth resulting from oral antibiotic use (which of itself causes translocation to MLNs only) and achieved systemic sepsis in this rodent model. In recent literature there exist reports of sepsis[92] and a sepsis-like syndrome resulting in death[93] after therapy with OKT3 (an anti-rejection drug given to transplant patients). This was postulated to have caused damage to GALT with release of lymphokines in addition to a generalized immune-suppressed state.

Deitch et al[94] have investigated the immunomodulatory effects of splenectomy on endotoxin-induced bacterial translocation and found that the incidence of translocation was unchanged after splenectomy in non-endotoxin-treated animals while those receiving endotoxin had a lower incidence of translocation if they had been splenectomized. These researchers theorized that splenectomy limits intestinal mucosal damage and down-regulates hepatic Kupffer cells which liberate translocation-promoting cytokines in response to endotoxin. The same group also investigated the effect of the immunoregulatory lymphokine interleukin 2 (Il-2) on cyclophosphamide-induced bacterial translocation[95] expecting to find a protective effect from Il-2. Instead, the incidence and numbers of isolated translocated bacteria were increased in the Il-2-treated mice whether

or not they were pre-treated with cyclophosphamide. Speculation was that the interleukin may have induced neutrophil chemotactic defects, exacerbated the cyclophosphamide-mediated decline in lymphocyte populations, or enhanced intestinal lymph flow thus delivering more bacteria to the MLNs.

A highly-regarded series of experiments in mice were carried out by Maddaus and Wells[96] in which the role of cell-mediated immunity in bacterial translocation was studied. By themselves, cyclosporine, anti-L3T4 antibody, and antithymocyte globulin were found to be unable to induce bacterial translocation. After monoassociation with *E. coli* (which always causes bacterial translocation to MLNs), congenitally T-cell deficient mice and mice treated with antithymocyte globulin showed higher numbers of enteric bacteria in MLNs. There was no significant spread beyond lymph nodes. In contrast to the aforementioned study by the Louisiana group[95], these researchers found that exogenous Il-2 decreased the overall incidence of translocation. The cause of this discrepancy has not been elucidated but could be due to differences in dosing and route of administration of Il-2. The conclusion of this study was that suppression of cell-mediated immunity has minimal influence on the mechanisms by which gut flora translocate to MLNs but suppression of cell-mediated immunity promotes increased survival of bacteria that have already reached the lymph nodes.

Cellular and humoral immune deficiencies may be present in a tumor-bearing organism. Thus, it would stand to reason that an animal with a malignancy would be more susceptible to the effects of bacterial translocation. To test this hypothesis, Berg and Penn[97] inoculated mice with viable sarcoma cells and followed their footpad delayed-type hypersensitivity reactions and serum hemagglutinins. Immune responses were diminished and translocation of enteric bacteria to MLNs, liver, kidney, and spleen was significantly increased in animals inoculated with sarcoma. The mechanism by which this occurred was not known but bacterial overgrowth and neutropenia did not occur. Further support of

the theory of tumor-enhanced translocation has been weak. A study of MLNs in humans undergoing resection of colorectal cancers[98] showed increased enteric flora in regional lymph nodes but this may have been due to mucosal breakdown by tumor. Patients with hematologic malignancies were followed to see if their fecal bacteria could predict the species of bacteria causing subsequent sepsis[99] but a causality between the leukemia and translocation was not clearly demonstrated. Souba showed that a tumor load deprives the gut of glutamine[100] and by this mechanism might be significant in promoting mucosal barrier breakdown.

Both burns and hemorrhage may cause immune suppression and are discussed in the respective sections on each.

E . Irradiation

In the 1950s, it was established that whole-body irradiation could lead to fatal infections from endogenous or exogenous organisms[101]. Radiation causes leukopenia and damage to the gut mucosa which have been shown to correlate with incidence of enteric bacteria in spleen, liver and blood[102]. However, a study by Guzman-Stein et al[27] showed that the presence of bacteria in mesenteric lymph nodes preceded detectable mucosal damage by 48 hours. Thus it has been theorized that a defect in macrophage function[103], or early endotoxemia[104] may be responsible, at least in part, for the sepsis seen in heavily irradiated animals. Souba et al. have been able to demonstrate a protective effect from glutamine on bacterial translocation in irradiated rats[83]. The mechanism for this is unclear and likely multifactorial with support of protein synthesis and lymphocyte function (see previous section on Glutamine).

F. Endotoxin

Perhaps the most extensively investigated precipitant of bacterial translocation and impairment to gut mucosal barrier function, has been bacterial cell wall lipopolysaccharide, or endotoxin. Almost all researchers in this field of study have carried out some experiments investigating its profound hyperdynamic physiologic and cellular metabolic effects. The loss of mucosal barrier function resulting from endotoxin makes possible the theory of translocation of bacteria from the intestinal lumen to MLNs as a sequelae of infection elsewhere in the body[17]. This might be important in the evolution of a minor infection to major polymicrobial sepsis. Conversely, it is also thought that endotoxemia may result from loss of mucosal barrier function[18]. Thus a question of cause or effect arises - does endotoxin precipitate loss of mucosal integrity resulting in translocation of bacteria, or does loss of gut barrier function result in endotoxin efflux? The answer remains a matter of controversy and likely a combination of the two processes occurs. It would seem that bacterial endotoxin increases the mucosal permeability, thus allowing further translocation of bacteria and endotoxin into the systemic circulation. This could mean that the endotoxic component of gram negative sepsis may have self-perpetuating capabilities.

Early studies of the passage of endotoxin from the gut into systemic circulation[105,106] showed that radiolabelled endotoxin passed from the intestinal tract into liver, kidney and spleen as a result of hypovolemic shock. The authors put forth the formulation that a variable amount of bacterial endotoxin is constantly produced by intestinal gram-negative bacteria. A small but significant fraction of this amount of endotoxin is absorbed continuously, probably at a variable rate, into the blood stream. In the normal animal, the endotoxin is rapidly and completely removed from the blood by

cells of the reticuloendothelial system. If the reticuloendothelial system is injured by hypoxia, deficient blood flow, colloidal blocking agents, radiation, intralipid, or other means, its ability to take up endotoxin and to detoxify it is reduced or lost so that the main defense of the host against bacterial endotoxin is damaged or destroyed[105]. The essence of this theory still holds true today[62].

Liberation of bacterial endotoxin is common after thermal or mechanical trauma[39,107], hemorrhagic shock[14,106], and other conditions leading to MSOF[108,109]. Sources of endotoxin in these clinical settings include the wound, gut, and visceral sites of infection such as lung[65]. The relative importance of these sources has not been adequately investigated.

Obstructive jaundice is also an established cause of endotoxemia generally felt to be the result of failure by the liver to clear the elevated quantities of endotoxin that leak from the gut into the portal circulation[110,111,112]. This elevation is thought to result from the absence of bile within the intestine which binds endotoxin[110], reduction in IgA which minimizes bacterial adherence[90], and bacterial overgrowth[36]. Thus four factors; hepatocyte dysfunction, diminished intraluminal endotoxin binding, decreased mucosal IgA, and bacterial overgrowth may all promote endotoxemia in this state.

Endotoxin has associated with it a variety of pathophysiologic effects. Beside producing the profound hemodynamic changes familiar in sepsis, it increases the permeability of the gut mucosa[113], increases vascular permeability, and impairs host immune defences[39]. It has been reported to activate the complement and coagulation systems[108] and produce oxygen free radical - mediated tissue injury[114]. Cecal bacterial population levels also rise temporarily after endotoxin[115]. It also increases mesenteric vascular resistance[116] which may contribute to increased mucosal permeability by way of ischemia and mucosal acidosis[22]. This effect may be attenuated by the pharmacologic

preservation of mesenteric blood flow[20]. The diminished blood flow of itself, however, is not sufficient to explain the increased enterocyte permeability as observed by Fink et al[117], when evidence of increased permeability was not demonstrated by mechanical reduction of blood flow to post-endotoxin levels. There would appear, therefore, to be other factors at play. A recent study by Deitch et al[118] found that early during endotoxemia, mesenteric blood flow was primarily impeded in the cecum and terminal ileum, while jejunal flow was relatively preserved. These results provide support for this group's previous findings of maximal mucosal damage in these areas after endotoxin challenge[9,39,65,115,119], as well as support for the findings by Fink et al[120] and others[116] of reduced mesenteric artery blood flow with normal or supernormal cardiac output in similar models. The exact mechanism by which endotoxin impairs host immunity is not well elucidated and dose, route and timing may alter the effect[121]. It is known, however, that endotoxin may suppress T-cell activation and stimulate interleukin-1 release[115].

The biochemical mediators of the endotoxin reactions are currently under study with macrophage-derived cytokines and arachadonic acid metabolites figuring prominently. Perhaps the most important mediator is tumor necrosis factor alpha (TNF). In 1988, Michie et al[122] showed a significant elevation in circulating TNF levels after endotoxin administration to humans. TNF is known to produce hemodynamic, hematologic, metabolic and pathologic changes similar to those illicited by endotoxin[123,124,125,126,127,128] and anti-TNF antibodies, or congenital inability to synthesize TNF, have been shown to be protective against the metabolic effects of endotoxin[129,130,131]. Anti-TNF antibody has, however, not been shown to prevent endotoxin-induced mucosal injury or disruption of gut flora ecology and the bacterial translocation associated with it[119]. Platelet activating factor (PAF) has been detected in plasma of endotoxin-treated animals and has been shown to be a mediator of gut mucosal

damage and increased vascular permeability in sepsis[123,132,133,134]. This phenomenon may be blocked by pretreatment with a PAF receptor antagonist[124]. Interestingly, the effects of TNF may also be blocked by a PAF receptor antagonist[123] suggesting that PAF may be the mediator by which TNF has its effect. Administration of a cyclooxygenase inhibitor (ibuprofen) in patients receiving endotoxin did not decrease TNF elevations but did have a significant attenuating effect on fever and endocrine responses suggesting that these effects of TNF are mediated via the cyclooxygenase pathway[122]. Another arachadonic acid metabolite-mediated response to endotoxin appears to be mesenteric hypoperfusion from splanchnic vasoconstriction, as evidenced by improved splanchnic blood flow in endotoxin-treated animals after treatment with a cyclooxygenase inhibitor[135] and by the same improvement after treatment with a leukotriene receptor antagonist[136].

One of the more extensively studied mediator systems in endotoxin-induced gut injury is the xanthine oxidase - oxygen free radical pathway[118,119,137,138,139]. This enzyme is present in gut epithelium and capillaries and causes generation of superoxide and hydrogen peroxide during periods of ischemia reperfusion and endotoxemia[22]. These free radicals are cytotoxic in their ability to oxidize sulfhydryl groups on proteins[140]. With inhibition of xanthine oxidase by allopurinol, tungsten, or dimethyl sulfoxide (DMSO), mucosal barrier damage can be reduced in an endotoxin-treated animal model resulting in a lower incidence of bacterial translocation[9,114]. The clinical importance of this mechanism must, however, be questioned due to findings of several studies. Firstly, an experiment by Redan et al[24] demonstrated translocation both in rats that had undergone ischemia without reperfusion, and rats that had undergone bowel manipulation alone without inflicted ischemia or reperfusion. Furthermore, the gut concentration of xanthine oxidase in humans is much lower than that seen in rodents[141,142,143].

Glutamine, as previously discussed, is the primary metabolic fuel of the small bowel. The effect of endotoxemia on small bowel glutamine utilization was studied by Souba et al[144] and it was discovered that glutaminase activity, and gut glutamine extraction and uptake from circulating and intraluminal sources[145], all fell after endotoxin administration, despite normal circulating glutamine levels. This is in contrast to surgical stress, in which intestinal glutamine consumption is elevated despite a fall in circulating levels[146]. The exact mechanism by which endotoxin causes these alterations in glutamine flux are unknown but likely to involve impaired intracellular metabolism and basolateral membrane transport[144] despite increased vesicle-mediated brush border uptake[147]. Deitch et al[39] investigated endotoxemia in protein malnourished mice and found a greater incidence and degree of bacterial translocation than from endotoxin alone. Malnutrition by itself was incapable of causing translocation. This effect is likely mediated by the systemic immunosuppressive effects of malnutrition combined with the effects of endotoxin. These experiments further the argument for adequate nutrition (preferably enteral) in the metabolically stressed patient.

To investigate the tissue distribution of translocated endotoxin, a study was carried out using burned mice gavaged with radiolabelled *E. coli* or *E. coli* endotoxin[18]. Translocation of whole bacteria was most common in the MLNs, spleen, lung and liver respectively with maximal bacterial killing detected in the MLNs. Isolated endotoxin concentrations were highest in the MLNs, liver, then lung respectively. This may be due to the fact that endotoxin is water-soluble and therefore may be protein-bound (which may also account for increased systemic uptake in burned animals resuscitated with albumin[148]). Thus studies measuring only detection of viable translocated bacteria in MLNs grossly underestimate the true extent of translocation of bacteria and ignore translocated endotoxin. The concentrations of translocated endotoxin were found to be well in excess of those needed to cause in vitro macrophage stimulation.

G. Hemorrhagic Shock

In the early years of research on gut barrier function, it was established that the splanchnic low-flow state induced by hypovolemic shock permitted the absorption of intraluminal toxic substances which could induce morbidity and mortality in the host[149]. Interest in this area waned until the mid 1980s when Berg and Deitch began experiments in this field, initially using stressors other than hypovolemic shock, due to the difficulty of controlling hypovolemia in the rodent model. One of the earliest studies of translocation in a pure hypovolemia model was by Koziol and Rush[150] in which unrestrained, unanesthetized rats were bled to a mean arterial pressure (MAP) of 30 mmHg for up to 7 hours, and then reinfused with shed blood. Blood cultures became positive for gut flora within 2 hours and progressed from mono- to polymicrobial over the following 48 hours post-shock despite persistently intact gut epithelium on histologic examination. This study was repeated by Baker and Deitch[151,152] using a 30, 60, or 90 minute shock period and again demonstrating enteric bacteria in blood and parenchymal organs with peak prevalence and density of translocated organisms found at 24 hours. Translocated bacterial population was noted to be directly proportional to the duration of hypovolemia, as was the extent of submucosal edema and focal necrosis. Over the following 6 days, it was noted that the animals cleared their organs of the translocated bacteria as they recovered from the shock. In other studies by Rush et al[153,154,155], it has been observed that lowered intestinal bacterial populations in antibiotic-treated or germ-free rats provide improved survival from sepsis in hypovolemic shock. Deitch et al[156] confirmed this in a similar model and demonstrated that findings were independent of mucosal permeability changes, as gut tissue of both conventional and antibiotic-treated animals showed similar increased enterocyte permeability after shock - likely due to disruption of tight junctions between epithelial cells. Also, the shock-induced microscopic

mucosal damage evidenced by submucosal edema and patchy necrosis was similar in the two groups.

Recent experiments have taken place to review the effects of different modalities of volume resuscitation on bacterial translocation. Reed et al[157] used a rat model bled to 30 mmHg for 30 minutes and then resuscitated with either shed blood, 3 % hypertonic saline and 50 % of shed blood, or 7.5 % hypertonic saline and 50 % shed blood. Their findings were of a significant reduction of bacterial translocation after 24 hours in animals resuscitated with hypertonic saline. The proposed explanation was of improved circulatory volume and reduction of splanchnic vasospasm. Morales et al[158] used a pig model bled to a MAP of 30-40 mmHg for 2 hours and then reinfused with whole blood or Ringers Lactate. After 48 hours, there was a greater incidence in translocation to liver and spleen in animals resuscitated with crystalloid but this did not reach statistical significance. The effects of various combinations of colloid and crystalloid on preserving gut mucosal barrier function after shock is a subject that merits further study.

Koziol's et al[150] original experiment, and a subsequent one using detection of hematogenous spread of a radioisotope from labelled ingested bacteria after shock[28], both concluded that the breakdown of gut barrier function occurred within 2 hours of the establishment of hypovolemic shock. This is supported by the work of Deitch[156]. The concept of bacterial translocation as an acute phenomenon (within 2 hours) and the extrapolation of conclusions to larger mammals and man, was challenged in an experiment carried out by Gelfand et al[51] in 1987. Swine were chosen for the model rather than rodents because pigs bear a better resemblance to man with respect to gastrointestinal and cardiovascular physiology (see. DISCUSSION - II. Swine Model). This study found no significant translocation of enteric bacteria into portal or systemic blood, mesenteric lymph or mesenteric lymph nodes within 6 hours of a shock from loss of 40% blood volume. In another study by the same group[158], translocation of enteric bacteria to MLNs occurred

in all instrumented control animals and in all shocked animals after 48 hours with sporadic spread to parenchymal organs. Thus we might conclude that in swine, translocation of enteric flora occurs between 6 and 48 hours after hypovolemic shock.

In contrast to this study, Rush et al[14] showed that in blood cultures drawn within 3 hours of admission to hospital in traumatized patients (with non-viscus injuries), those patients with admission blood pressures of < 80 mmHg had a 56 % rate of positive blood cultures (66 % of which contained gram negative bacteria) while that of those with admission blood pressure of > 110 mmHg was 4 % (all gram positive). Problems with this study were small sample sizes, lack of proof that the organisms were gut-derived, and the fact that sepsis-related and MSOF outcomes were not discussed. A similar study by Moore et al[159] demonstrated a high (75 %) mortality in trauma patients arriving in an emergency department with shock (systolic BP < 90 mmHg) and bacteremia, and a 100 % mortality in those arriving in shock with gram negative bacteremia. Less than half of these patients had hollow viscus injury, therefore at least some infections were considered to be from translocated organisms.

The exact mechanism by which hypovolemic shock allows failure of the gut mucosal barrier remains an active subject of research. The most obvious effect of shock is a local ischemia due to reduced blood flow. This is most pronounced at the tips of the mucosal villi, which are particularly susceptible to low flow due to the hairpin loop arrangement of villus capillaries[160] and their perpendicular takeoff from supplying arterioles. This provides a 'skimming' effect that reduces the effective hematocrit of blood entering the villus capillary[161]. It is also well-established that during periods of hypovolemia, splanchnic bed perfusion is reduced out of proportion to the decrease in total cardiac output[162], likely mediated by the renin-angiotensin axis[163]. With ischemia there is a breakdown of the tight junctions[156] and the development of patchy necrosis, both of which likely facilitate physical movement of bacteria and endotoxin. Cytotoxic

oxygen free radicals are generated from intestine-associated xanthine oxidase in ischemia-reperfusion injury in rats. These radicals may be scavenged by dimethyl sulfoxide or deferoxamine[137], or their generation may be inhibited by tungsten or allopurinol pretreatment[134]. A reduction of oxygen free-radicals decreases the number of organisms translocating to MLNs in this model. It is likely no coincidence that xanthine oxidase activity is highest at the tips of the villi[138], which is where most mucosal injury/edema is seen microscopically[137]. Another mechanism by which hypovolemic shock may induce mucosal damage, is through the oxygen free radical mediated activation of the complement cascade, with subsequent C5a formation which increases vascular permeability, enhances smooth muscle contraction, and releases histamine from mast cells[164]. Thromboxane A_2 is also activated (as evidenced by a rise in its metabolite, Thromoboxane B_2) after shock[164].

Hemorrhagic shock is, in of itself, immunosuppressive. This has recently been demonstrated by measuring lymphocyte response to T-cell mitogen in endotoxin-resistant mice[165], which was markedly depressed on the first day after hemorrhage and required 10 days to return to pre-shock levels. Allogenic mixed lymphocyte reaction was also reduced for 9 days after shock and when measured 3 days post-shock, 72 hour mortality as a result of cecal ligation and puncture was 100 % vs. 58 % in animals not previously shocked. The precise mechanism of immune suppression after hypovolemic shock is not well understood but likely aspects include depressed macrophage antigen presentation, enhanced Kupffer cell capacity for TNF production[166], and impaired lymphocyte proliferation[167]. It has also been demonstrated in mice that the gut's capacity for absorption of d-xylose is reduced at 2 and 4 hours after hemorrhagic shock and that this effect may be reversed by administration of diltiazem[168], which also improves macrophage function after shock[169].

H. Human Studies

It is important to bear in mind that almost all studies of bacterial translocation and gut-associated MSOF have been carried out using animal models. These have been primarily rodents whose metabolism differs from larger mammals and humans. A few investigators have carried out experiments in sheep, dogs, and in pigs which bear a closer metabolic similarity to humans. Due to the nature of the patient population experiencing bacterial translocation and MSOF, randomized, prospective, and controlled studies in humans have been understandably difficult to carry out.

In 1987, Border et al[10] published a prominent study of an extensive collection of data from patients with blunt trauma in which it was postulated that gut bacteria and endotoxin play an important role in determining the outcome of traumatized patients. This, and other studies[14,62,170,171] have suggested that there exists a phenomenon of bacterial and/or bacterial endotoxin translocation in traumatized humans. A recent prospective study by Moore et al[61] attempted to follow the development of MSOF in 20 severely traumatized patients by measuring portal blood cultures, endotoxin, complement, TNF, and Il-6. Despite the eventual development of MSOF in 30% of the patients, no significant portal bacteremia or mediator changes could be measured in portal blood over the 5 day post-injury sampling period. The authors acknowledge that the enteric lymphatic route of bacterial spread remains in question. A followup study by the same investigators sampled cultures of blood , mesenteric lymph node, and liver in 147 acutely injured patients requiring laparotomy and found that all of those with shock and enteric bacteremia subsequently died[159]. A study by Rush et al[14] also demonstrated acute bacteremia in 53% of trauma patients with hypotension and no hollow viscus injury. Again, this group displayed the highest mortality rate.

Another study[172] sampled mesenteric lymph nodes in critically ill patients undergoing emergency laparotomy but again found no significant nodal infection. Problems with this study include the use of preoperative antibiotics, short hypotensive periods, and early sampling (perhaps not allowing enough time for translocation to occur). Recently, Braithwaite et al[173] examined immunofluorescence as a method of detecting killed and phagocytosed bacteria in mesenteric lymph nodes in trauma patients and found evidence of killed bacteria in all lymph nodes despite negative tissue cultures (unpublished data). The significance of this finding is as yet uncertain as it raises question of whether translocation to lymph nodes is an normal ongoing process that gets amplified in response to physiologic stress thus overloading the normal reticuloendothelial response to result in MSOF.

Both Deitch et al[57] and Wilmore et al[56] have examined the effects of burn injury on the translocation of an inert compound, lactulose, from the gut. Both found that permeability of the gut to lactulose increased acutely in burned patients as well as when the severity of infection in the patient increased. Wilmore's group also carried out a study of enteral lactulose permeability after administration of bacterial endotoxin to human volunteers[21]. Those receiving endotoxin displayed a significant increase in lactulose absorption and excretion. These results may be considered significant if we assume that bacteria and endotoxin are able to penetrate the gut mucosa in the same manner as lactulose. The same experimenters also measured TNF levels in volunteers receiving endotoxin and found a significant elevation in the experimental group as opposed to controls[122]. These studies demonstrate a relationship between endotoxin, gut permeability, and TNF in humans.

I. Attenuation

To give further insight into the mechanism of translocation, several investigators have carried out experiments looking at ways of reducing or minimizing the bacteria which move from the gastrointestinal tract in response to injury. In a rodent model of endotoxin-induced translocation, Deitch et al[9] demonstrated a reduction in the quantity of bacteria isolated from mesenteric lymph nodes in animals pre-fed a tungsten-supplemented diet and in animals pre-fed an allopurinol supplemented diet. Both allopurinol and tungsten have been shown to reduce xanthine oxidase activity and neither affected cecal bacterial populations.

In a porcine model of thermal injury, Herndon et al[48] demonstrated a reduction in the incidence of translocation to mesenteric lymph nodes and solid organs in animals treated with a thromboxane synthetase inhibitor (OKY-046) immediately before and for 16 hours after burn injury. The OKY-046 treated animals demonstrated a lesser degree of reduction of superior mesenteric artery blood flow in response to burn injury. This is the postulated mechanism by which translocation was inhibited. This theory was similarly tested by Jones et al[174] in a rodent burn model with significant reduction in the incidence of gut bacteria isolated from mesenteric lymph nodes when a 5 day course of an angiotensin converting enzyme inhibitor (enalapril) was given before thermal injury. Again, the maintenance of splanchnic perfusion was considered to be the mechanism of the protective effect of enalapril.

In their established rodent models of bacterial translocation, Deitch et al have also demonstrated species-specific[65,88] and strain-specific[175] variation in susceptibility to gut injury by burn and endotoxin. This has been highly suggestive of a genetic predisposition to translocation which they believe is due to different levels of xanthine oxidase activity.

As discussed earlier, glutamine plays an important role in the maintenance of gut barrier function. It has been demonstrated that in rats, oral supplementation of diet with glutamine results in a significantly lowered incidence of bacteremia following an endotoxin challenge[176] and, in another model of radiation enteritis, reduced the incidence of bacterial translocation to mesenteric lymph nodes[83]. Another compound known to simulate pancreatic and gut mucosal growth, bombesin, has also been shown to reduce the incidence of bacterial translocation to mesenteric lymph nodes in thermally injured rats[177].

An active area of research at present is the potential use of antibodies directed at the molecules responsible for bacterial translocation and sepsis. Recently, anti-TNF antibodies have been introduced into the armamentarium of agents with potential to ameliorate translocation and its consequences[130]. Early studies demonstrated a survival benefit from pretreatment of a baboon model of endotoxic shock with TNF antibody[178]. Surprisingly, these anti-TNF antibodies were not shown to reduce endotoxin-induced mucosal injury and bacterial translocation in one study[119]. An anti-endotoxin antibody has also been developed and is undergoing testing[179]. Early studies of its use have shown improved survival in sepsis[180,181]. Similarly, PAF antagonists are undergoing development and testing[182].

Another currently active area of research in the prevention of gut-derived sepsis in critically ill patients has been selective decontamination of the gastrointestinal tract. The practice of eliminating pathogens at their source makes intuitive sense but raises concerns of selection for and overgrowth of pathogenic organisms resistant to the antimicrobial agents used in decontamination[3,183]. Furthermore, although a definite reduction in the incidence of colonization and infection is seen in clinical trials[184], reduced morbidity and mortality have been inconsistently demonstrated [3,185]. A recent trial of selective gut decontamination in 31 severely burned patients showed a decline in septicemia and

death[118]. Despite the lack of strong clinical evidence, animal studies[33,35] have suggested a reduction of stress-induced bacterial translocation resulting from selective decontamination by preserving GI anaerobic flora and reducing populations of gram negative aerobic bacilli. Considering these mixed reviews, the true efficacy of this often expensive clinical maneuver remains uncertain.

J. Mechanisms

In experimental studies to date, bacterial translocation across an intact intestinal epithelium has been difficult to visualize microscopically and the precise anatomic mechanism still remains somewhat unclear. Microbes have been demonstrated in the lamina propria in areas of ulceration at the tips of villi after hemorrhagic shock in rats[134]. More specifically, Wells et al[186] have utilized immunofluorescent microscopy to demonstrate *Enterococcus fecalis* organisms within columnar epithelial cells, lamina propria, submucosa and muscularis externa in a model of translocation caused by bacterial overgrowth. Using transmission electron microscopy on the same samples, they visualized coccal bacteria within vacuoles in the cytoplasm of intact epithelial cells suggesting that the bacteria translocate through, and not between enterocytes. Using this technique of identification, sampling of gut mucosa was carried out over the length of the gastrointestinal tract in these mice demonstrating a preponderance of translocating microbes in cecal and colonic mucosa as opposed to stomach and small bowel[187], thus indicating the lower bowel as the primary site for translocation of enteric bacteria. Earlier work by this group[19,103] strongly suggested that macrophage transport of intraluminal particles to lymph nodes was likely. This theory has been neither refuted nor conclusively proven. In fact, the two mechanisms are not mutually exclusive. As it is known that

macrophages are a site of synthesis and release of several cytokines, the presence of bacteria within these cells would seem a reasonable mechanism for activation of the inflammatory mediators which characterize the septic state. Once bacteria have been transported to mesenteric lymph nodes, they may remain viable there for up to four days. Other investigators have noted penetration of bacteria through the junctional complex and into the intercellular spaces of the intestinal epithelium[188].

Recently, Alexander et al[16] have undertaken to examine the process using Candida, radiolabelled *E. coli*, and radiolabelled *E. coli* endotoxin in a burned guinea pig model. Electron microscopy demonstrated intercellular transport of Candida as early as 1 hour after burn injury, with clear demonstrations of brush border internalization and basement membrane externalization of intracellular organisms. In the lamina propria, Candida could be seen in the process of being phagocytosed with the greatest proportion of intramacrophage yeast in deeper regions. Similar findings were seen with *E. coli* and *E. coli* endotoxin.

Bacterial translocation to MLNs occurs after many stressors of varying severity. Quite often, despite the presence of these intranodal organisms, the host does not develop sepsis and die. Therefore, it may be concluded that there exists a mechanism (likely immunologic) whereby these microfoci of infection are cleared. It has also been postulated[13,88,97] that indigenous bacteria continuously cross the mucosal barrier to localize in the MLNs of unstressed, healthy animals where they are eliminated by host immunity and therefore are not cultured experimentally. Only in times of immune system compromise, and either physical damage to the mucosa, or bacterial overgrowth, is the immune system overloaded such that enteric bacteria can be cultured from parenchymal organs or blood. The discovery of bacteria in MLNs is very common after even minor insults such as intestinal handling[24,189], and these organisms are likely in the process of being eliminated by host defences. These theories are supported by several studies in

unstressed animals in which intestinal bacteria were isolated from inert intraperitoneal prosthetic materials[190] and experimentally induced intra-abdominal abscesses[189]. In a model of burn injury[40], bacteria were isolated from mesenteric lymph nodes and parenchymal organs, with a significantly greater frequency 48 hours after injury than at 96 hours. This suggested that organisms were cleared from these tissues by the host's oun immunity. Similar findings have been seen in rats undergoing hypovolemic shock in which incidence and counts of bacteria in MLNs was higher one day after shock than 2 or 7 days later. This was also observed by Deitch et al[115] in a model of endotoxemia. In monoassociated mice[88], they found that the addition of a burn wound significantly impaired the host's ability to clear MLNs and splanchnic organs of bacteria. Translocated bacteria were cultured for up to 4 days after the burn, whereas they were cleared after 1 day in non-burned animals. It has been shown that *E. coli* which have translocated after intestinal overgrowth, are capable of surviving for up to 4 days in MLNs after eradication of this organism from the bowel[191], suggesting that the duration of actual translocation may be kinetically different from the time of recovery. To summarize, it has been postulated[18] that bacteria may translocate acutely, but those that do are quickly killed. Those organisms which are detected experimentaly, therefore, likely have translocated later, after the GALT system for clearance has been somewhat exhausted.

VI. TWO - HIT THEORY

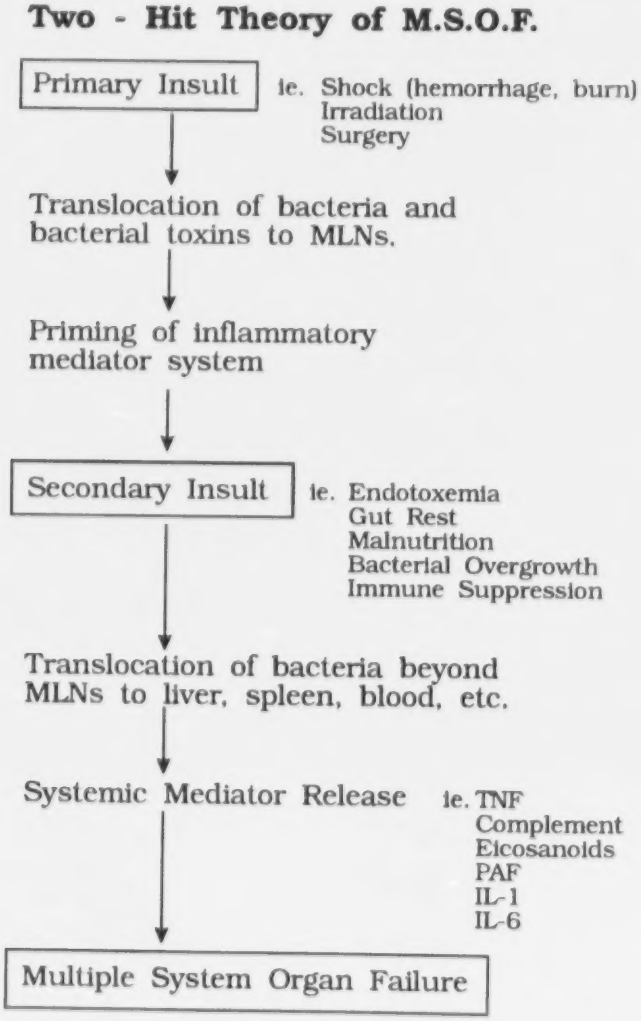
In many of the studies cited, translocation of bacteria takes place from the gut into mesenteric lymph nodes only. However, under certain conditions that sufficiently impair the host's defense systems, bacteria can spread beyond the MLNs and cause systemic infection. Such situations include high-dose endotoxemia[65], prolonged intestinal obstruction[38], and greater than 40 % body surface area burn[46]. More commonly, however, spread of infection beyond MLNs occurs when the model is subjected to more than one stressor. The theory that an initial insult primes the organism in such a way that a subsequent challenge has a more pronounced effect than expected, is referred to as the 'two hit phenomenon'[3].

The concept of a combination of physiologic stresses resulting in organ failure has been alluded to for many years. In 1977, Polk et al[192] described how post-operative patients in whom intra-abdominal infection developed, displayed a higher rate of organ failure. These patients experienced the stress of surgery, followed by that of their infection. In 1983, Faist et al[170] suggested a distinction between a "single-phase organ failure" which results from trauma and shock, and a more slowly developing "two-phase organ failure" which results from trauma, shock, and sepsis. The two-phase organ failure was more common and carried a higher mortality. While the single-phase organ failure results from the injury itself and is dependent on the effectiveness of resuscitation, two-phase organ failure is more familiar in the post-operative or burn patient in the intensive care unit.

These and other models of multiple systemic injuries imply that there exists a priming and activation sequence of cytokine-releasing cells (neutrophils and macrophages)

whereby a noninjurious (or mildly injurious) stimulus sets the stage, such that the additional stimulus provided at a later time will result in an amplified response with release of sufficient mediators to cause tissue injury[2,193]. It is possible that the second inflammatory stimulus need not be overwhelming, merely persistently greater than the host's ability to clear it[3]. Similarly, the priming stimulus also may not need to be profound. Multisystem organ failure might then result from the enhanced subsequent activation of inflammatory mediators. This theory is illustrated in Figure 1.

Figure 1.



It is the purpose of this research project to investigate this theory as it applies to hemodynamic changes and bacterial translocation following two stressors commonly encountered in the traumatized patient, namely hypovolemic shock, followed by endotoxin.

V. SUMMARY

The gastrointestinal tract is now regarded as a metabolically active [62], immunologically important[63], and bacteriologically decisive[39,10,171] organ in critical illness. These features reflect the complex interaction of ischemia, cytokines, nutrients, endotoxin, oxygen free radicals and a host of other pathophysiologic mechanisms, some of which remain to be discovered. The loss of the gastrointestinal tract's ability to act as a barrier between its toxic and infectious contents and the sterile internal milieu of the organism, has been identified as an integral part of the development of MSOF in critically ill and injured patients. When this occurs, bacterial or bacterial endotoxin translocation takes place. According to Deitch[194] the criteria for bacterial translocation include: 1. altered permeability of the intestinal mucosa, 2. impaired host immunologic function, and 3. disruption of the normal indigenous enteric flora (with overgrowth of one or more species). This review encompasses only a small portion of the myriad of experiments that have been carried out to provide a better understanding of bacterial translocation.

EXPERIMENTAL DESIGN

The purpose of this experiment is to determine if a physiologic stressor does in fact "prime" an animal in such a way that a second stressor, administered after a period of recovery, brings about a different response in the subject when compared to similar animals in whom the first stressor is not given. Although it has been alluded to in the literature, actual testing of response to sequential physiologic injuries has not been carried out in a large animal model. Response to the second insult could be of a greater magnitude in previously stressed animals due to a response system which has already been "turned on", or it could be of a lesser degree due to a response system that has been partially exhausted by the first insult. Results of such an experiment would either support the Two-Hit Theory (if a difference were seen), or refute it (if no difference were seen). In order to simulate physiologic insults commonly encountered in a clinical setting, a hemorrhagic shock was chosen as the first event, followed by an infusion of endotoxin 48 hours later. This would be much like a patient who is brought to hospital with musculoskeletal trauma, resuscitated, and then develops infection from indwelling catheters and cannulae.

Based on information presented thus far, the following null and alternate hypotheses have been formulated:

NULL HYPOTHESIS

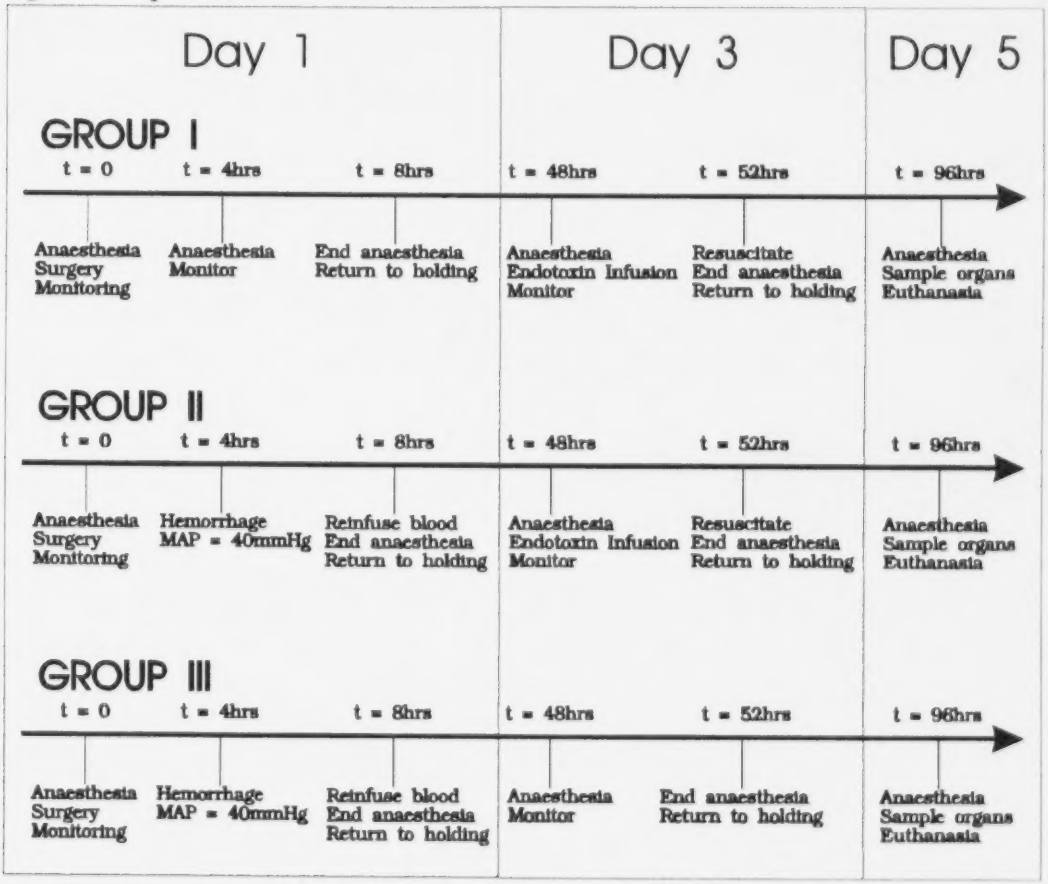
An initial injury (hemorrhagic shock) does not predispose to an altered physiologic response when a second insult (endotoxic shock) is administered after a period of recovery (48 hours).

ALTERNATE HYPOTHESIS

An initial injury will bring about an atypical physiologic response to a second insult given after a period of recovery from the first injury.

In order to test the hypothesis, the following experiment was carried out in a swine model:

Figure 2. Experimental Time Schedule



VARIABLES TO BE MEASURED: blood pressure, heart rate, central venous pressure, craniomesenteric artery flow, FiO_2, serum endotoxin, glucose, lactate, cortisol, hemoglobin, arterial and portal venous blood gases, cultures of blood and organs

MATERIALS AND METHODS

I. Animal Preparation

Thirty female swine were purchased (one at a time) from one supplier (M. Boris, Leduc, Alberta) whose animals are of a strain which has a subnormal incidence of malignant hyperthermia, a condition known to be common in domestic swine[195]. They were fed an antibiotic-free diet at the Biomedical Animal Facility for two weeks and then brought to the main research facility (Surgical Medical Research Institute) three days prior to experimentation. Pigs were all Landrace cross-bred with White York and weighed between 30 and 40 kg on the first day of the experiment. All were fasted for 12 hours before the experiment. Randomization was not performed as animals were from an uncontrolled source. They were assigned in an alternating manner to one of the three experimental groups.

On the morning of Day 1 of the experimental run, each animal was brought to the operating laboratory and an intramuscular dose of Ketamine Hydrochloride (Ketalean, 25mg/kg, MTC Pharmaceuticals, Cambridge, Ontario) was administered to produce a light sedation. Atropine sulfate (Atropine, 0.05mg/kg IM, Abbott Laboratories Limited, Montreal, Quebec) was also given to reduce respiratory secretions. Anaesthesia was then induced with isofluorane (Forane, 3%, Anaquest, Mississauga, Ontario) by face mask inhalation and an intravenous catheter (Flash-Cath, #18 Gauge, Travenol Laboratories Inc., Deerfield, Illinois) was inserted in an ear vein and secured. At this point, a baseline blood culture was taken. During the cervical dissection phase of surgery, an infusion of Ringer's Lactate (Lactated Ringer's Injection, Baxter Corporation, Toronto, Ontario) at

2.0 ml/kg/hr was maintained using an automated volumetric infusion pump (Imed 960, Imed Let., England) and during laparotomy, this was increased to 10 ml/kg/hr.

The animals were then placed, in the supine position, on the operating table, and intubated with a cuffed endotracheal tube (7.0mm internal diameter, Portex). Correct endotracheal tube placement was ensured with auscultation. The dose of Isofluorane was then reduced to 2% and pressure ventilation was commenced at a tidal volume of 10-15 ml/kg at 12-15 breaths/min; inspiratory:expiratory ratio 1:2 (Fraser Harlake anesthesia ventilator; Fraser Sweatman Inc; Orchard Park, NY). Ventilator settings were adjusted according to results of arterial blood gas determinations throughout the course of the anaesthesia period. Tidal volume and respiratory rate were adjusted in efforts to maintain a partial pressure of carbon dioxide of arterial blood (P_aCO_2) at 37-43 mmHg. The fraction of inspired oxygen (FiO_2) was adjusted to maintain the partial pressure of oxygen of arterial blood (P_aO_2) between 150-200 mmHg.

Electrocardiograph patches (Red Dot, 3M, London, Ontario) were placed on the torso near the right and left forelegs, and the left hindleg. Leads were connected to a preamplifier (Model 78203C, Hewlett Packard) equipped with a stripchart recorder (Model 7754A, Hewlett Packard) and heart rate was recorded. A sigmoid tonometer (Tonometrics Inc. , Worcester MA. USA) was placed per rectum and introduced to a length of 30 cm and secured in place with tape. Normal saline (4 ml) was instilled into the tonometer balloon and allowed to equilibrate with luminal gas pressures for at least 90 minutes. A digital thermometer (Model 8500-40, Cole Parmer, Chicago, Illinois) probe was also placed in the rectum and body temperature monitored. The animal's body temperature was maintained between 36.5-38.5 ^oC using a heating/cooling blanket (Aquamatic Thermia Model RK-200, Gorman - Rupp Industries Inc., Bellville, Ohio) placed on the operating table under the animal. The normal resting body temperature of a pig is reported to be 39 ^oC[196].

II. Surgical Procedures

A. Aseptic Technique

The nature of this study required aseptic technique at all times, and unless otherwise stated, can be assumed.

Sterilization of the surgical field was attained by way of a 5 minute scrub preparation with chlorhexidine gluconate 4 % solution (Hibitane, Ayerst Laboratories, Montreal, Quebec) followed by two paintings with povidone-iodine 10 % (Betadine Solution, Purdue Frederick Inc., Toronto, Ontario). The area was allowed to dry after each of these three treatments and was then draped in a sterile manner.

All equipment in contact with the animal was sterilized prior to use by one of three methods. New equipment in sealed packages was already sterilized, usually by ionizing radiation. All other equipment was carefully washed with soap and water, and packaged. Heat-resistant equipment was steam sterilized at 121 ^{o}C for one hour. Plastics, and other heat-sensitive materials were gas sterilized with ethylene oxide for one hour and forty-five minutes, then aerated for twelve hours. This equipment was carefully flushed with sterile saline to remove any remaining gas prior to its use.

B. Carotid Artery and External Jugular Vein Catheterization

With the pig in a left lateral position, an 8 cm transverse incision was made in the right side of the neck 2 cm cephalad to the shoulder girdle. By dissecting between muscle bellies, the external jugular vein was readily identified and dissected free along a 5 cm length. Continuing deeply toward the posterior of the trachea, the right carotid sheath

was encountered and opened exposing a length of carotid artery. Two long catheters were made by placing intravenous catheters (Flash-Cath, #14 Gauge, Travenol Laboratories Inc., Deerfield, Illinois) into the lumens of two 55 cm lengths of silastic tubing (Silastic Medical Grade Tubing, 0.062 in. ID, Dow Corning, Midland, Michigan). These catheters were tunnelled into the incision from the dorsal midline at a point between the scapulae. Each of the vessels was ligated and a catheter introduced proximally, by a small transverse arteriotomy/venotomy, and secured in place. By inserting a 15 cm length into each vessel, the tip of the arterial and venous catheters were located at the level of the arch of the aorta and the superior vena cava respectively. This was done in an effort to avoid catheter clotting later in the experiment. Each catheter was then fitted with a heparin lock cap (PRN Adapter, Becton Dickinson, Sandy, Utah) and flushed with a dilute solution of heparin sodium (Organon Teknika, 1000 unit/ml., Toronto, Ontario) made up to 1 unit/ml with normal saline. The incision was then closed in two layers with a deep running suture of braided polyglycolic acid (3-O Dexon Plus, Davis and Geck, Montreal, Quebec) followed by a running subcuticular suture of braided nylon (2-O Surgilon, Davis and Geck, Montreal, Quebec).

Catheters were connected to pressure transducers (Model 1290A, Hewlett Packard), preamplifiers (Model 78205B, Hewlett Packard), and a stripchart recorder (Model 7754A, Hewlett Packard). Equipment was zeroed according to manufacturer's instructions and central venous pressure and mean arterial pressure were monitored.

C. Abdominal Operation

After closure of the cervical incision, a small incision was made in the dorsal midline at the level of the umbilicus and a subcutaneous tunnel was extended ventrally from this incision to a second similar incision made at the costal margin. A subcutaneous

pocket was formed around this lateral incision. A third catheter similar to those used in the neck was introduced from a point 1 cm ventral to the dorsal midline incision and brought through the subcutaneous tunnel and coiled up in the lateral subcutaneous pocket. An 8 mm ultrasonic flow probe (T-101, Transonics Inc., Ithaca, New York) was placed in a similar fashion leaving the electrical connector protruding through the skin on the dorsum. The two incisions were then closed leaving the catheter and flow probe coiled in a lateral subcutaneous position.

The animal was then placed supine and the abdomen repreped and redraped. A midline incision was made and the peritoneal cavity entered. The subcutaneous pocket containing the coiled flow probe and catheter was then entered from inside the abdominal cavity and these two appliances were delivered into the abdomen. The defect through which they were passed was then tightly closed with sutures to prevent hernia formation.

The small and large bowel were then delivered into the wound and the inferior edge of the tail of the pancreas mobilized to reveal the craniomesenteric artery at its origin from the abdominal aorta. The flow probe was then positioned around the artery and secured in place.

The bowel was returned to the abdomen and an accessible mesenteric venous tributary was selected, dissected free and ligated. Through a transverse venotomy, the catheter (with the tip cut at 90 degrees) was then introduced to a point where it was palpable in the portal vein at the level of the hepatoduodenal ligament. This maneuver was found to be helpful when drawing blood from the catheter in that it prevented it from sucking up against the side wall of the portal vein.

The abdomen was then closed in two layers using braided polyglycolic acid for fascia (O Dexon Plus, Davis and Geck, Montreal, Quebec) and subcuticular braided nylon (2-O Surgilon, Davis and Geck, Montreal, Quebec) for skin. At the completion of the

laparotomy, the intravenous infusion of Ringer's Lactate was decreased to a maintenance level of 2.0 ml/kg/hr. This rate was kept constant throughout the remainder of the anaesthetic period. Animals were allowed to stabilize for one hour after closure of the laparotomy.

III. Hemorrhagic Shock

At this point in the experiment, called T=4 hr, monitoring was begun and animals assigned to Group II (n=6) or to Group III (n=5) underwent a four hour period of hemorrhagic shock in which the mean arterial pressure (MAP) was lowered to 40 mmHg (+/- 3 mmHg). This was achieved over a 30 minute period by withdrawing blood from the jugular venous catheter and collecting it in sterile blood bags containing anticoagulant / citrate / phosphate / dextrose / adenine solution (CPDA-1)(Fenwal Laboratories, Division of Baxter Travenol Laboratories of Canada Ltd., Malton, Ontario). Shed blood was reinfused as necessary to maintain desired blood pressure during the shock. At the end of the shock period, blood was reinfused through a blood filter set (2C2141 Y-Type Blood-Solution Administration Set and Pressure Pump, Travenol Laboratories Inc., Deerfield, Illinois). Group I animals were simply left under anaesthesia for the four hour period.

At T=8 hr., anaesthesia was discontinued and the endotracheal tube, thermometer, tonometer and ECG leads were removed. Incisions were dressed with gauze and tensor bandages. Catheters were left in place after being capped and flushed with heparinized saline. When awake, animals were then transported to holding cages at the research facility where they were provided food and water ad lib. Analgesia consisted of buprenorphine hydrochloride (0.02 mg/kg IM q12h, Buprenex, Reckitt and Colman, Pharmaceutical Division, Kingston-upon-Hull, England) for 3 doses the first of which was given immediately upon arrival at the holding cage.

Arterial blood samples (6ml) were drawn from the arterial catheter every 12 hours for bacterial culture throughout the remainder of the experiment. Vascular catheters were flushed with heparin (Organon Teknika, 1000 unit/ml., Toronto, Ontario) made up to 100 units/ml with normal saline, at these collection intervals in order to maintain patency.

IV. Endotoxic Shock

At T=47 hr., animals from Group I (n=6) and Group II (n=6) were again anaesthetized in the same fashion as used on the first day of the experiment. Endotracheal tube, thermometer, tonometer, ECG, and pressure transducers were all placed as before. The ultrasound flow probe was also connected to a monitor (T201 2-Channel Ultrasonic Bloodflow Meter, Transonics Systems Inc.) coupled to a personal computer (AT 486/SX 25MHz, Intelligent Personal Computers, Toronto, Ontario). Intravenous Ringer's Lactate was again given by continuous infusion at a rate of 2 ml/kg/hr.

At T=48 hr., endotoxin (25 mcg/kg, Escherichia coli lipopolysaccharide, Serotype 0111:B4, Sigma Chemical Co, St. Louis, Missouri) was infused into the portal venous catheter over a period of 30 minutes. Animals were then monitored for a four hour period as during hypovolemic shock. After the endotoxic shock period, resuscitation with Ringer's Lactate was given as needed to achieve pre-shock blood pressure. Anaesthesia was then discontinued, monitors removed and disconnected, and the animal returned to the holding cage. Again, q12h blood cultures were taken.

Animals from Group III (n=5) underwent four hours of monitored anaesthesia with maintenance Ringers Lactate only from T=48 to T=52 (control group).

V. Tissue Sampling

Forty-eight hours after the second anaesthetic period (T=96), animals were once again returned to the laboratory and anaesthesia was again achieved using the same technique as before. With the pig in the supine position, the abdomen and thorax were prepped and draped as previously done for the laparotomy. The laparotomy incision was re-opened and tissue specimens measuring roughly 1 cm^3 were taken for culture. Organs sampled included liver, spleen, kidney, and three mesenteric lymph nodes from areas draining jejunum, ileum, and colon. The left hemithorax was then entered though a 10 cm lateral thoracotomy and a specimen of lung tissue taken for culture.

VI. Euthanasia

Unless already dead, animals were sacrificed after organ sampling with an intravenous infusion of pentobarbital (0.5 ml/kg Euthanyl; pentobarbital 240 mg/ml, propylene glycol 0.20 ml/ml, MTC Pharmaceutical, Cambridge, Ontario). Death then occurred within 20 seconds.

VII. Monitoring During Shock Periods

From T=4 to T=8, and from T=48 to T=52, animals were monitored in two general categories; hemodynamic and biochemical/hematological. Bacteriological monitoring took the form of blood cultures drawn q12h from the beginning of each animal (T=0) to just before re-opening the laparotomy to sample organs for culture at the end of the experiment (T=96).

In general, measurements are given in SI units. However, in instances where SI units have little clinical use, this has purposely been omitted. An example of this would be reporting mean arterial pressure in mmHg. To report this information in kilopascals, the proper SI unit for pressure, would be in marked contrast to the clinical setting in North America and the world literature[197].

A. Hemodynamic Monitoring

The following measurements were taken at specified intervals during the hemorrhagic shock period (T=4 to T=8)(Table 2) and considered under the general heading of hemodynamic measurements:

Table 2. - Hemodynamic Parameters and Time Schedule of Measurements - Day 1

	Time (hours)								
Parameter	4	4.5	5	5.5	6	6.5	7	7.5	8
HR	X	X	X	X	X	X	X	X	X
CVP	X	X	X	X	X	X	X	X	X
MAP	X	X	X	X	X	X	X	X	X
CAF	X	X	X	X	X	X	X	X	X
FiO_2	X	X	X	X	X	X	X	X	X
Weight	X								

During the endotoxic shock period (T=48 to T=52), hemodynamic measurements were recorded as follows:

Table 2. - Hemodynamic Parameters and Time Schedule of Measurements - Day 3

	Time (hours)										
Parameter	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
HR	X	X	X	X	X	X	X	X	X	X	X
CVP	X	X	X	X	X	X	X	X	X	X	X
MAP	X	X	X	X	X	X	X	X	X	X	X
CAF	X	X	X	X	X	X	X	X	X	X	X
FiO_2	X	X	X	X	X	X	X	X	X	X	X

A. Heart rate (HR) was measured as described above, and reported as beats per minute (bpm).

B. Mean Arterial Pressure (MAP) was measured directly from the indwelling right internal carotid catheter as displayed by monitoring equipment and reported in mmHg.

C. Central Venous Pressure (CVP) was measured directly from the indwelling right external jugular venous catheter as displayed by monitoring equipment and reported in mmHg.

D. Craniomesenteric Arterial Flow (CAF) was measured using the ultrasonic flow probe previously described. Data was reported in ml/min/kg, by dividing the measured flow by the animal's weight in order to compensate for size variation in animals.

E. Fraction of inspired oxygen (FiO_2) was recorded directly from the setting of the oxygen blender on the ventilator apparatus and is reported in per cent.

F. Weights were measured the morning of surgery, using the same scale each time, and reported in kilograms (kg).

B. Biochemical / Hematological Monitoring

During the two shock periods, T=4 to T=8 and T=48 to T=52, blood samples were taken from the indwelling catheters at regular intervals and the following measurements were made:

Table 4 - Biochemical / Hematological Monitoring and Time Schedule of Measurements

Parameter	Time (hours)								
	4	4.5	5	5.5	6	6.5	7	7.5	8
	48	48.5	49	49.5	50	50.5	51	51.5	52
P_aO_2	X	X	X	X	X	X	X	X	X
P_aCO_2	X	X	X	X	X	X	X	X	X
$[H^+]_a$	X	X	X	X	X	X	X	X	X
HCO_{3a}	X	X	X	X	X	X	X	X	X
S_aO2	X	X	X	X	X	X	X	X	X
P_pO_2	X	X	X	X	X	X	X	X	X
P_pCO_2	X	X	X	X	X	X	X	X	X
$[H^+]_p$	X	X	X	X	X	X	X	X	X
SpO_2	X	X	X	X	X	X	X	X	X
Hgb	X	X	X	X	X	X	X	X	X
C_aO_2	X	X	X	X	X	X	X	X	X
DO_{2g}	X	X	X	X	X	X	X	X	X
C_pO_2	X	X	X	X	X	X	X	X	X
$C_{a-p}O_2$	X	X	X	X	X	X	X	X	X
VO_{2g}	X	X	X	X	X	X	X	X	X
O_2ER_g	X	X	X	X	X	X	X	X	X
pH_i	X	X	X	X	X	X	X	X	X
Endotoxin	X	X	X	X	X	X	X	X	X
Lactate	X	X	X	X	X	X	X	X	X
Glucose	X	X	X	X	X	X	X	X	X
Cortisol	X	X	X	X	X	X	X	X	X

A. Partial pressure of Oxygen in arterial blood (P_aO_2) was measured from samples obtained from the carotid artery catheter, and reported in mm Hg. This blood was drawn into a heparinized syringe, and kept on ice until run through an electrode type automated pH and blood gas analyzer (IL 1306 pH/Blood Gas Analyzer - Instrumentation Laboratory, Lexington, Massachusetts). Samples were run within 15 minutes of being drawn.

B. Partial pressure of Carbon Dioxide of arterial blood (P_aCO_2) was measured from the same sample, using the same apparatus, and reported in mm Hg.

C. Hydrogen ion concentration of arterial blood ($[H^+]_a$) was calculated from the same arterial sample, using the same blood gas analyzer. The machine reported results in pH, and this was converted to $[H^+]_a$, in nmol/L, using the formula:

$$[H^+] = \text{antilog } (-pH)$$

D. Bicarbonate (HCO_{3a}), in mmol/L, was calculated from the carotid arterial sample by the blood gas analyzer.

E. Oxygen saturation of samples of carotid arterial blood (S_aO_2), in percent, was measured by the blood gas analyzer.

F. Portal venous blood was sampled within 1 minute of arterial blood. A sample was collected in a heparinized syringe and run through the blood gas analyzer in the same manner as arterial blood. This analysis yielded measurements of the partial pressure of oxygen (P_pO_2) of portal blood.

G. The portal venous hydrogen ion concentration ($[H^+]_p$) was also determined by the blood gas analyzer.

H. The portal venous blood oxygen saturation (S_pO_2) was also determined by the blood gas analyzer.

I. Hemoglobin (Hgb), in grams per decilitre (g/dl), was measured from the arterial sample only, using and automated photoelectric device (M4 30 Coulter Counter, Coulter Electronics Inc., Hialeah, Florida).

J. Oxygen content of arterial blood (C_aO_2), in ml O_2/dl, was calculated using the formula:

$$C_aO_2 = (1.34 \times S_aO_2 \times Hgb) + (0.0031 \times P_aO_2)$$

Where: 1.34 = Amount of Oxygen bound to hemoglobin when fully saturated (in ml O_2/dl)

0.0031 = Amount of Oxygen dissolved in blood (in ml O_2/dl/mm Hg)

K. The rate of delivery of oxygen to the gut (DO_{2g}) was calculated using the formula:

$$DO_{2g} = (C_aO_2 \times CAF)/100 \qquad (100 = \text{correction factor for units})$$

L. Oxygen content of portal blood (C_pO_2), in ml O_2/dl, was calculated using the same formula as for C_aO_2, substituting P_pO_2 for P_aO_2, and S_pO_2 for S_aO_2.

M. The arterial-portal venous oxygen content gradient ($C_{a\text{-}p}O_2$), in ml O_2/dl, was calculated using the formula:

$$C_{a\text{-}p}O_2 = C_aO_2 - C_pO_2$$

N. The rate of uptake of oxygen by the gut (VO_{2g}) was calculated as the product of the arterial-portal venous oxygen content difference and the craniomesenteric arterial flow.

$$VO_{2g} = (C_{a\text{-}p}O_2 \times CAF)/100 \qquad (100 = \text{correction factor for units})$$

O. The oxygen extraction ratio of the gut was calculated as follows:

$$O_2ER_i = VO_2/DO2$$

Therefore $O_2ER_i = (C_{a\text{-}p}O_2 \times CAF)/(C_aO_2 \times CAF) = C_{a\text{-}p}O_2/C_aO_2$

P. The sigmoid colon mucosal pH (pH_i) was calculated from the Henderson Hasselbach equation using the PCO_2 of a saline sample from the sigmoid tonometer. This was done according to techniques set forth by Dr. Fiddian-Green[74] which assume that intraluminal bicarbonate concentration equals arterial bicarbonate concentration, and that the pK of tissue fluid is the same as that of plasma. CO_2 is freely diffusible between tissue fluid, cells, the lumen of the gut, and the tonometer balloon. Therefore:

$$pH_i = pK_a + \log ([HCO_3^-{}_a]/PCO_{2t}) \qquad (pKa = 6.1)$$

Q. Endotoxin was measured by use of quantitative chromogenic assay kits (Biowhittaker QCL-1000, BioWhittaker Inc., Waldersville, Maryland 21793) which have been utilized by other investigators[14] and found to provide satisfactory results. A Limulus lysate amoebocyte reagent prepared from horseshoe crab circulating amebocytes is combined with a plasma sample and, after incubation, a stop reagent is added. When exposed to minute amounts of endotoxin, the lysate increases in opacity as well as viscosity and may gel depending on the concentration of endotoxin. The mechanism by which this occurs is not completely understood. Comparison to a standard is carried out using a spectrophotometer (Unicam SP 1800 Ultraviolet Spectrophotometer, Pye Unicam Ltd., Cambridge, England) to provide quantitative data.

R. Serum lactate levels were measured using a Stat-Pack™ Rapid Lactate Test (Behring Diagnostics Inc., Sommerville, New Jersey 08876). This test is based on the following reactions: L-lactate and NAD combine in the presence of LDH to

form pyruvate and NADH. The pyruvate is removed from the reaction with L-glutamate in the presence of glutamate pyruvate transaminase forming L-alanine and alpha-ketoglutarate. This assay was then quantified using a spectrophotometer (Multistat III Instrumentation Laboratory Micro Centrifugal Analyzer - Instrumentation Laboratory, Lexington, Massachusetts 02173).

S. Glucose levels were measured using a Beckman Astra 8 Automated STAT/Routine Analyzer (Beckman Instruments Inc. , Diagnostic Systems Group, Brea, California 92621). This analyzer utilizes an oxygen rate method involving an oxygen electrode, reagent, and an electronic system which measures the rate of change in oxygen consumption when a sample is injected into an enzyme reagent solution. When this happens, beta-D-glucose from the sample combines with dissolved oxygen from the solution forming gluconic acid and hydrogen peroxide (glucose oxidase catalyzed). In this reaction, oxygen is consumed at the same rate as glucose and the negative slope of the oxygen consumption curve (rate of oxygen depletion) is directly proportional to the concentration of glucose in the sample thus allowing electronic extrapolation to a glucose level. Reversal of the reaction is prevented by adding ethanol to the reaction which combines with hydrogen peroxide (via. catalase) to produce acetaldehyde and water.

T. Serum cortisol levels were measured at the University of Alberta Hospital Biochemistry Department (Endocrinology Division). An Enzymun-Test Cortisol (Boehringer Mannheim, France) competitive binding assay was used which employs a tube coated with oxamino bovine serum albumin conjugate antibody. This enzyme-linked immunosorbent assay (ELISA) is read with data reduction on a Boehringer Mannheim ES 300 spectrophotometer.

C. Bacteriological Monitoring

Blood (6 ml) was drawn for culture every 12 hours during the experiment. The first sample (T=0) was drawn from the ear vein that was cannulated for infusion of crystalloid at the beginning of the experiment. Subsequent samples were drawn from the indwelling arterial catheter. Arterial samples were chosen over venous to avoid possible clearance of gut-derived bacteria by the macrophages of the systemic circulation[14]. Aliquots of 3 ml were injected into aerobic (Bactec NR6A Culture Vial, Becton Dickinson Diagnostic Instruments System, Towson, Maryland) and anaerobic (Bactec NR7A Culture Vial, Becton Dickinson Diagnostic Instruments System, Towson, Maryland) culture vials.

All culture vials were then taken to the Microbiology Laboratory at the University of Alberta Hospital, and placed through an automated blood culture analyzer (Bactec 860, Becton Dickinson Instruments System, Towson, Maryland). This self-contained unit incubated all samples at 37 ^{o}C. Each vial was sampled to determine the amount of carbon dioxide produced, and if significant, the vial opened and plated on the following media:

1. Blood Agar in Carbon Dioxide
2. Brain heart Infusion
3. Chocolate Agar

In addition, a gram stain was performed. All vials were sampled twice a day for the first forty-eight hours, and then once a day for the next five days. Lack of significant carbon dioxide production by this time, was interpreted as no growth. All positive cultures were read by one individual (L. C. Vandenborn), who was blinded as to which group the animal was assigned.

At the end of the experiment (T=96 hr), lung, liver, kidney, spleen, and three mesenteric lymph nodes were sampled in a sterile manner using fresh sterile instruments to dissect each sample. Previous studies have shown that enteric flora can be found in all of these organs following sufficient physiologic stress[31,56]. Roughly 1 cm^3 of tissue was taken for each specimen and placed into a sterile sample jar (StarPlex Scientific, item 3009, Etobicoke, Ontario) and sealed. Tissue samples were processed by the Microbiology Laboratory of the University of Alberta Hospital. Specimens were ground in a sterile fashion and plated onto media:

1. Blood Agar (Carbon Dioxide)
2. McKonkey Agar
3. Brain Heart Infusion (Anaerobic)
4. Phenyl Ethyl Alcohol (Anaerobic)
5. Blood Agar (Anaerobic)

A gram stain was done. Plates were observed for two to five days, depending on the medium. The same process for identification was used for tissues as for blood cultures. The fact that this system of microbial culture and identification is in clinical use in a large medical centre is testimony to its accuracy.

VIII. Statistical Method

All laboratory data was coded and entered into a computer (AT 486/SX 25MHz, Intelligent Personal Computers, Toronto, Ontario) running a Microsoft Excel (Version 3, Microsoft Corporation) spreadsheet program. Descriptive statistics and frequencies were

determined for each treatment group by an independent statistician (Dr. M. Grace - University of Alberta). Primary comparisons were completed at times when maximal differences between groups were apparent and are reported in the analysis. For the most part, groups of animals were compared at the final data collection time (T=8) on Day 1, and at T=48.5 and T=52 on Day 3. Comparisons were made by an analysis of variance with multiple range test and the Fischer's protected least significant difference (LSD) test. A Fisher's exact test was used for bacteriologic data. The level of significance was taken as $p<0.05$ or less where stated.

RESULTS

I. Exclusion / Dropout Criteria and Mortality

Although thirty animals were entered into the study, useable data was obtained from only seventeen. Animals were dropped out of the experiment before completion of the full five days only if they died. This occurred with unfortunate frequency mainly due to technical errors in anaesthesia and ventilator management by the experimenter. A single death occurred due to operative technique when the animal developed a ventral hernia several hours after surgery. This narrow-necked hernia was located at the point where the flow probe wire and portal venous catheter had been brought into the peritoneal cavity from the lateral subcutaneous pocket. A loop of small bowel became incarcerated and the animal succumbed due to bowel obstruction. In animals subsequent to this event, the abdomen was closed more securely. The first animal used in the experiment was excluded because halothane was used as an anaesthetic (instead of isofluorane), because the endotoxic shock (Day 3) was followed for only three hours before resuscitating the animal, and because the portal venous catheter was non-functional.

Other animals were excluded after completion of the experiment based on bacteriologic findings suggestive of infection derived from causes other than the experimental shocks. These included aspiration pneumonia due to profuse vomiting during recovery, an omphalomesenteric cyst, and one animal with a community-acquired campylobacter diarrheal illness (had diarrhea even before initial surgery).

Two unexplained deaths occurred. One animal never regained consciousness after discontinuation of anaesthetic at the end of the Day 1 shock. Although the animal was normotensive, normocardic and well oxygenated, it would not breathe spontaneously nor

would it maintain its own airway. Death ensued at discontinuation of ventilation after several hours off anaesthetic. A cerebrovascular event was suspected but was not identified on necropsy (performed by Dr. N. Nation, Veterinary Pathologist - University of Alberta, Health Sciences Laboratory Animal Services). The other unexplained death occurred during the night of the first experimental day. The animal appeared well at the time of the T=12 blood culture, but was found dead the following morning. Necropsy was performed by the veterinary pathologist but a cause of death could not be discerned.

A single death occurred during the endotoxic shock on Day 3. This animal had undergone hemorrhagic shock on Day 1 (Group II) and had a profound cardiovascular collapse shortly after completion of the endotoxin infusion. This was considered to be a significant event in support of the alternate hypothesis as this was the only animal that died in response to the experimental stresses.

During the time period of T=4 to T=8 (Day 1), biochemical samples were not drawn from four if the six animals in Group I. This was done in order to save on laboratory expenses. Hemodynamic values during this period were similarly not recorded although the animals remained stable under anaesthesia. The two animals from this group that were monitored were considered to be a satisfactory representation of the (non-stressed) animal under anaesthesia during this time.

Tables of data are shown for parameters measured in animals from each of the three groups. Group I received anaesthetic only from T=4 to T=8 (Day 1), then endotoxin infusion from T=48 to T=52 (Day 3). Group II were put into hemorrhagic shock from T=4 to T=8 (Day 1), and also received endotoxin infusion over 30 minutes at T=48 and were monitored until T=52 (Day 3). The animals in Group III had hemorrhagic shock from T=4 to T=8 (Day 1), and anaesthetic only from T=48 to T=52 (Day 3). At the bottom of each graph, at each 15 or 30 minute interval, the average (Mean), standard

deviation (Std.Dev.), and standard error of the mean (S.E.M.) are given. Results are depicted graphically in cases where discernable patterns were detected. Mean values from each point in time are plotted with error bars depicting the S.E.M. . Results from Group I are plotted as squares, Group II as diamonds, and Group III as triangles. This convention will be maintained for all graphs.

II. Hemodynamics

In this section, the results of monitoring of the following parameters will be tabulated for each experimental group: heart rate, central venous pressure, mean arterial pressure, craniomesenteric artery flow rate, fraction of inspired oxygen, and animal weight. These measurements were taken at specified intervals (Table 2. and Table 3.) and are depicited in graph form in cases where a notable difference exists between experimental groups. Results will be discussed and statistical comparison applied where appropriate.

Although body temperature was measured, it was artificially kept within the range of 36.5 - 38.5 ^{o}C using the heating/cooling blanket and therefor not worthy of presentation in any detail. The cumulative intravenous fluid administration is also not reported as the maintenance rates of 2 ml/kg/hr during cervical cutdown and shocks, and 10 ml/kg/hr during laparotomy were strictly adhered to. As no urinary catheter was placed, urine output was not measured.

A. Heart Rate

Heart rates (HR) during Day 1 (T=4 to T=8) are depicted graphically (Figure 3). At the time of initiation of hemorrhage (T=4), Group I animals had a HR of 114 ± 13 bpm, Group II animals had a rate of 100±18, and Group III were at 110±11 bpm ($p > 0.05$). Over the time interval of the hemorrhagic shock, Group II and Group III animals mounted a tachycardia which was significantly different ($p < 0.05$) from Group I animals at T=8. The heart rate of control animals did not increase during this period.

Figure 3. Heart Rate for T=4 to T=8 (Day 1) - Hemorrhage

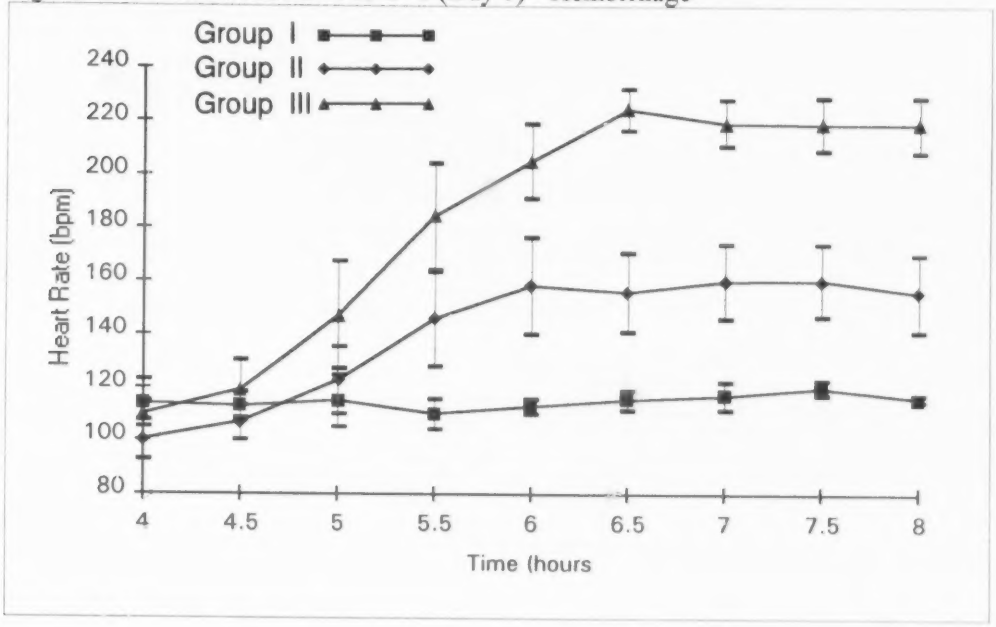


Table 5. Heart Rate (bpm) for Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	105	108	105	104	110	112	112	117	115
26	123	118	125	116	116	119	122	123	117
Mean	114	113	115	110	113	115.5	117	120	116
Std.Dev.	12.7	7.1	14.1	8.9	4.2	5.0	7.1	4.2	1.4
S.E.M.	9.0	5.0	10.0	6.0	3.0	3.5	5.0	3.0	1.0

Table 6. Heart Rate (bpm) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	128	126	160	180	178	170	180	197	190
9	110	118	126	166	198	184	200	188	200
11	91	92	93	98	104	106	120	121	112
29	103	100	120	173	187	183	180	174	160
15	78	88	84	83	101	115	115	122	127
17	91	117	154	175	182	177	165	160	145
Mean	100.2	106.8	122.8	145.8	158.3	155.8	160.0	160.3	155.7
Std.Dev.	17.5	15.6	30.9	43.4	43.8	35.6	34.8	32.6	34.7
S.E.M.	7.2	6.4	12.6	17.7	17.9	14.5	14.2	13.3	14.2

Table 7. Heart Rate (bpm) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	112	153	189	208	222	230	219	208	200
24	114	104	118	157	173	226	230	228	244
27	118	124	191	231	239	244	246	250	244
28	90	84	87	120	170	197	200	216	206
30	115	130	150	206	221	225	201	192	201
Mean	109.8	119	147	184.4	205	224.4	219.2	218.8	219
Std.Dev.	11.3	26.2	45.1	45.0	31.4	17.1	19.6	21.8	22.9
S.E.M.	5.0	11.7	20.2	20.1	14.1	7.6	8.8	9.7	10.3

Endotoxin was infused into Group I and Group II animals from T=48 to 48.5 (Day 3). All groups started from a similar HR at T=48, and the Group III animals maintained a fairly steady rate for the four hour period. In contrast, the Group I animals developed an early and persistent tachycardia (ANOVA, $p < 0.01$) which was significantly greater than that of Groups II and III at T=48.5 ($p < 0.01$). The Group II animals, however, showed less increase in HR (ANOVA, $p < 0.05$), which also took much longer to begin than in their Group I counterparts and was not statistically different from Group I or Group III at T=52.

Figure 4. Heart Rate for T=48 to T=52 (Day 3) - Endotoxin Infusion

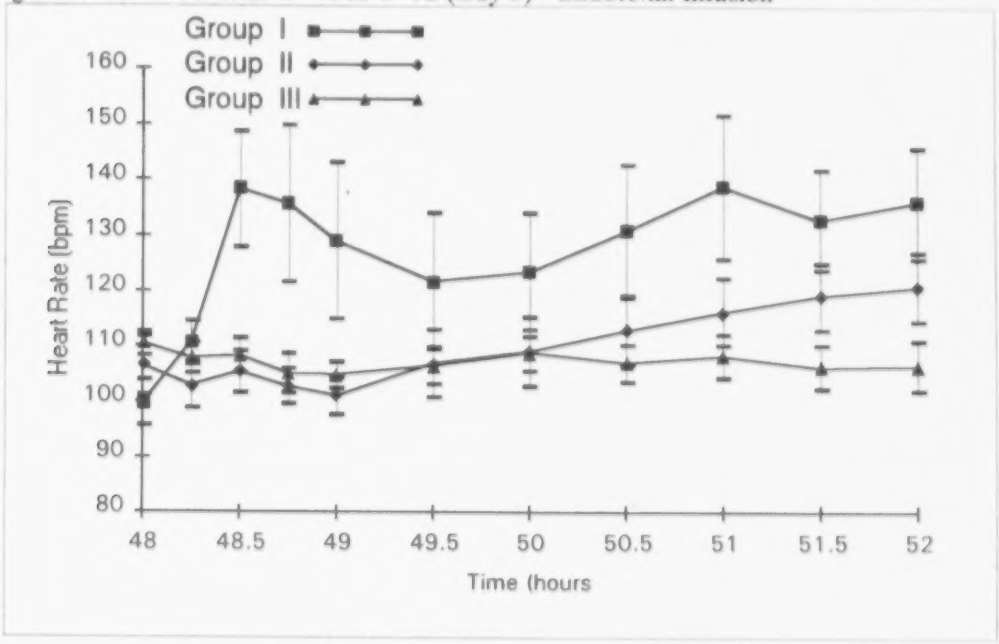


Table 8. Heart Rate (bpm) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
7	85	101	168	188	193	176	166	176	180	160	176
8	108	124	170	152	139	138	145	155	169	156	148
10	112	120	123	117	117	100	108	124	146	134	138
14	100	103	114	108	114	104	106	104	111	118	123
25	101	110	139	153	116	110	115	120	123	125	127
26	92	106	116	96	95	102	101	106	104	104	104
Mean	100	111	138	136	129	122	124	131	139	133	136
Std.Dev.	10.0	9.4	25.3	34.6	34.3	30.1	26.1	28.7	31.3	21.9	24.6
S.E.M.	4.1	3.8	10.3	14.1	14.0	12.3	10.6	11.7	12.8	8.9	10.0

Table 9. Heart Rate (bpm) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
5	90	92	98	93	93	115	123	116	115	128	121
9	114	110	108	104	100	94	90	90	100	105	115
11	127	120	122	112	105	112	121	133	141	140	147
29	99	97	100	95	97	105	104	112	115	117	120
15	103	99	98	111	98	90	96	110	114	105	106
17	106	99	106	101	113	125	120	116	112	120	115
Mean	107	103	105	103	101	107	109	113	116	119	121
Std.Dev.	12.8	10.3	9.2	7.9	7.1	13.2	14.3	13.8	13.4	13.6	14.0
S.E.M.	5.2	4.2	3.8	3.2	3.2	6.0	6.4	6.2	6.0	6.1	6.2

Table 10. Heart Rate (bpm) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
20	110	103	101	102	105	110	110	107	100	96	92
24	111	109	114	110	102	100	102	110	106	105	110
27	114	112	110	99	101	104	108	100	116	112	113
28	102	100	100	98	102	100	104	100	100	100	101
30	115	115	116	116	114	118	120	118	119	118	116
Mean	110	108	108	105	105	106	109	107	108	106	106
Std.Dev.	5.1	6.2	7.4	7.8	5.4	7.7	7.0	7.6	8.9	8.9	9.8
S.E.M.	2.3	2.8	3.3	3.5	2.4	3.4	3.1	3.4	4.0	4.0	4.4

B. Mean Arterial Pressure

The mean arterial pressure (MAP) from T=4 to T=8 is given for Group I (Table 11), Group II (Table 12) and Group III (Table 13). Animals from Group II and Group III were bled to a MAP of 40 mmHg over the first 30 minutes of the experimental run, and kept at that level (with very fluctuation) for the remainder of the four hours. Group I animals maintained a steady MAP over the four hours.

Figure 5. Mean Arterial Pressure for T=4 to T=8 (Day 1) - Hemorrhage

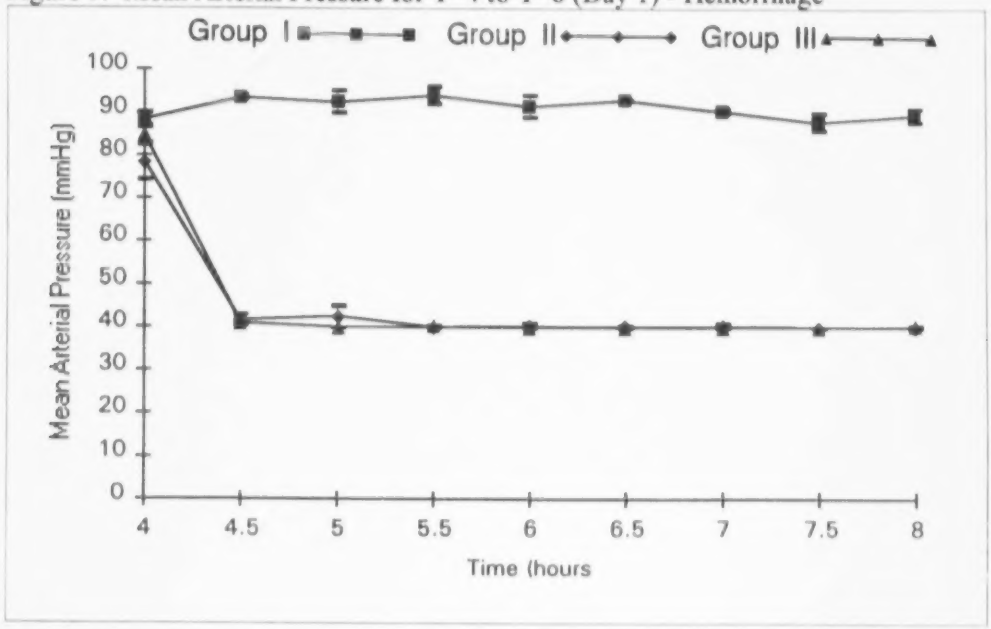


Table 11. Mean Arterial Pressure (mmHg) of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	87	93	90	92	89	93	91	86	88
26	90	94	95	96	94	93	90	90	91
Mean	88.5	93.5	92.5	94	91.5	93	90.5	88	89.5
Std.Dev.	2.1	0.7	3.5	2.8	3.5	0.0	0.7	2.8	2.1
S.E.M.	1.5	0.5	2.5	2.0	2.5	0.0	0.5	2.0	1.5

Table 12. Mean Arterial Pressure (mmHg) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	93	47	55	40	42	41	42	40	40
9	85	43	40	40	40	40	40	40	40
11	65	40	40	40	40	40	40	40	40
29	81	40	40	40	40	40	40	40	40
15	73	40	40	40	40	40	40	40	40
17	74	40	40	40	40	40	40	40	40
Mean	78.5	41.7	42.5	40.0	40.3	40.2	40.3	40.0	40.0
Std.Dev.	9.9	2.9	6.1	0.0	0.8	0.4	0.8	0.0	0.0
S.E.M.	4.1	1.2	2.5	0.0	0.3	0.2	0.3	0.0	0.0

Table 13. Mean Arterial Pressure (mmHg) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	84	42	40	40	40	40	40	40	40
24	90	42	40	40	40	40	40	40	40
27	86	41	40	40	40	40	40	40	41
28	80	40	40	40	40	40	40	40	40
30	84	40	40	41	40	40	40	40	40
Mean	84.8	41	40	40.2	40	40	40	40	40.2
Std.Dev.	3.6	1.0	0	0.5	0	0	0	0	0.5
S.E.M.	1.6	0.5	0	0.2	0	0	0	0	0.2

The changes in blood pressure on Day 3 were different among the three groups as shown in Figure 6. Group I animals (Table 14) responded to the endotoxin by initially entering a hyperdynamic phase with a transient elevation of MAP above baseline from T=48 to T=48.5 with a mean maximum of 109±22 mmHg. During this period, Group II (Table 15) animals did not display this hyperdynamic response, but rather, their MAP immediately fell to a mean of 58±25 mmHg at T=48.5 ($p < 0.001$ compared to Group I). Throughout the rest of the endotoxic shock period, the Group II animals maintained a lower MAP than Group I but this did not reach statistical significance. The Group III

animals (Table 16) maintained a steady MAP with insignificant deviation from the baseline over the four hours. At T=52, the MAP of Group III (89±6 mmHg) was statistically different from both Group I ($p < 0.05$) and Group II ($p < 0.01$).

Figure 6. Mean Arterial Pressure for T=48 to T=52 (Day 3) - Endotoxin Infusion

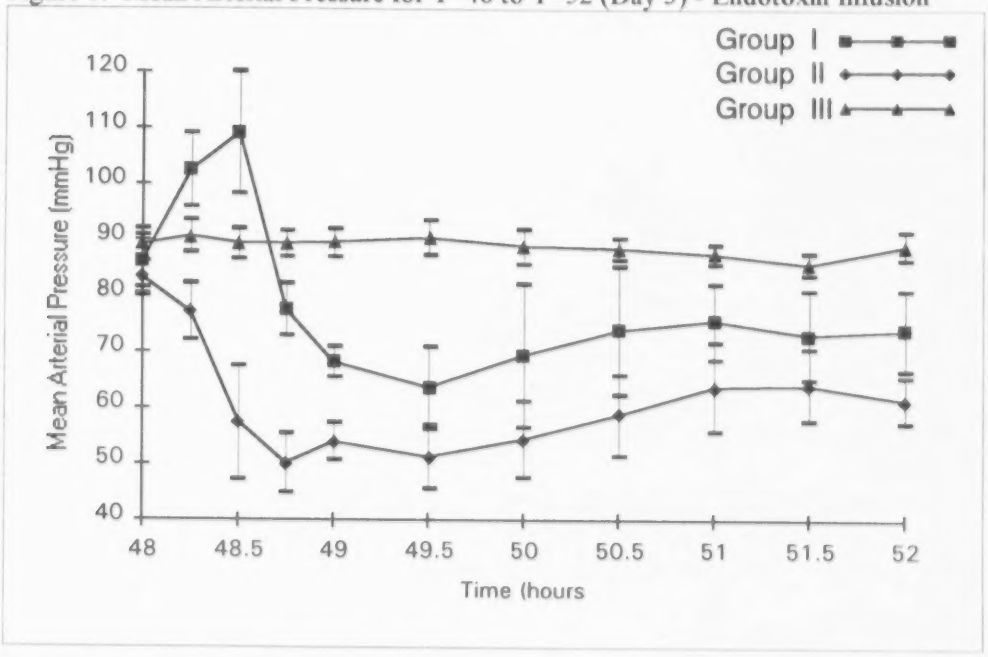


Table 14. Mean Arterial Pressure (mmHg) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
7	90	109	115	85	76	83	109	112	96	98	100
8	80	95	70	67	70	77	88	89	88	83	73
10	91	104	118	87	70	45	40	52	74	53	61
14	73	80	100	65	61	50	48	52	60	64	64
25	100	118	129	84	63	61	62	67	68	67	67
26	84	109	123	78	69	66	70	72	68	74	79
Mean	86.3	102.5	109.2	77.7	68.2	63.7	69.5	74.0	75.7	73.2	74.0
Std.Dev.	9.4	13.3	21.5	9.5	5.4	14.8	25.7	23.2	13.7	15.8	14.3
S.E.M.	4.7	6.7	10.8	4.8	2.7	7.4	12.8	11.6	6.8	7.9	7.1

Table 15. Mean Arterial Pressure (mmHg) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
5	87	80	50	48	48	43	45	50	53	59	60
9	88	92	94	72	67	74	84	90	90	76	67
11	71	63	32	40	52	43	50	60	81	86	75
29	82	75	54	52	54	56	54	56	60	61	62
15	82	64	35	35	46	41	40	43	47	48	48
17	90	89	80	54	57	51	54	54	52	55	57
Mean	83.3	77.2	57.5	50.2	54.0	51.3	54.5	58.8	63.8	64.2	61.5
Std.Dev.	6.9	12.2	24.8	12.9	7.5	12.5	15.4	16.3	17.5	14.1	9.1
S.E.M.	2.8	5.0	10.1	5.3	3.4	5.6	6.9	7.3	7.8	6.3	4.1

Table 16. Mean Arterial Pressure (mmHg) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
20	84	87	84	83	86	82	83	84	82	80	83
24	87	90	91	93	84	86	87	89	86	84	90
27	96	97	90	94	96	99	98	94	92	89	86
28	83	82	84	84	87	90	83	85	90	86	88
30	96	97	98	93	95	95	94	91	88	90	98
Mean	89.2	90.6	89.4	89.4	89.6	90.4	89	88.6	87.6	85.8	89
Std.Dev.	6.4	6.5	5.8	5.4	5.5	6.8	6.8	4.2	3.9	4.0	5.7
S.E.M.	2.9	2.9	2.6	2.4	2.5	3.0	3.0	1.9	1.7	1.8	2.5

C. Central Venous Pressure

Day 1 central venous pressures (CVP) are given for Group I (Table 17), Group II (Table 18), and Group III (Table 19). Group I animals stayed almost constant over the four hours while those animals undergoing hemorrhage (Group II and Group III) showed a precipitous fall over the first 30 minutes to remain at 0 mmHg from T=5 to T=8.

Table 17. Central Venous Pressure (mmHg) of Group I Animals for T=4 to T=8 (Day 1) -Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	4	4	4	4	3	3	3	2	2
26	3	3	3	4	3	3	3	3	3
Mean	3.5	3.5	3.5	4	3	3	3	2.5	2.5
Std.Dev.	0.7	0.7	0.7	0	0	0	0	0.7	0.7
S.E.M.	0.5	0.5	0.5	0	0	0	0	0.5	0.5

Table 18. Central Venous Pressure (mmHg) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	4	2	0	0	0	0	0	0	0
9	3	1	0	0	0	0	0	0	0
11	3	0	0	0	0	0	0	0	0
29	3	0	0	0	0	0	0	0	0
15	4	0	0	0	0	0	0	0	0
17	3	0	0	0	0	0	0	0	0
Mean	3.3	0.5	0	0	0	0	0	0	0
Std.Dev.	0.5	0.8	0	0	0	0	0	0	0
S.E.M.	0.2	0.3	0	0	0	0	0	0	0

Table 19. Central Venous Pressure (mmHg) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	4	0	0	0	0	0	0	0	0
24	4	0	0	0	0	0	0	0	0
27	4	2	0	0	0	0	0	0	0
28	3	0	0	0	0	0	0	0	0
30	3	0	0	0	0	0	0	0	0
Mean	3.6	0.4	0	0	0	0	0	0	0
Std.Dev.	0.6	0.9	0	0	0	0	0	0	0
S.E.M.	0.2	0.4	0	0	0	0	0	0	0

During the endotoxic shock of Day 3, the animals' CVP responses were similar to those of their MAP. All groups showed a significant decline (ANOVA $p < 0.05$) over the four hour period. The Group I animals (Table 20) showed an initial hyperdynamic phase with a maximum CVP of 5.8±3 mmHg reached at T=48.5 , followed by a fall to zero and near-zero levels. Group II (Table 21) CVPs did not increase initially, but declined over the first 30 minutes to 2.5±1.5 mmHg at T=48.5. This was statistically different from Group I ($p < 0.05$). Group III animals (Table 22) maintained a relatively near-baseline CVP which was significantly different from both Group I and Group II from T=49 to T=52 ($p < 0.01$).

Figure 7. Central Venous Pressure for T=49 to T=52 (Day 3) - Endotoxin Infusion

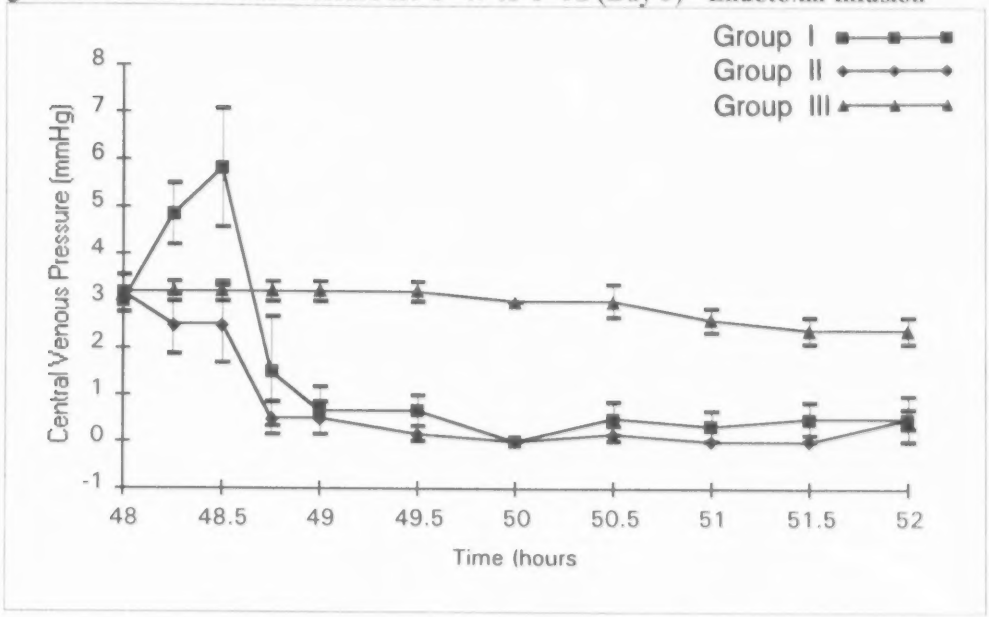


Table 20. Central Venous Pressure (mmHg) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
7	3	5	2	0	0	1	0	0	0	0	0
8	4	5	3	0	0	1	0	0	0	1	0
10	3	5	8	0	0	0	0	0	0	0	0
14	3	2	5	0	0	0	0	0	0	0	0
25	2	7	10	7	3	2	0	1	0	0	0
26	3	5	7	2	1	0	0	2	2	2	3
Mean	3.0	4.8	5.8	1.5	0.7	0.7	0	0.5	0.3	0.5	0.5
Std.Dev.	0.6	1.6	3.1	2.8	1.2	0.8	0	0.8	0.8	0.8	1.2
S.E.M.	0.3	0.7	1.3	1.2	0.5	0.3	0	0.3	0.3	0.3	0.5

Table 21. Central Venous Pressure (mmHg) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
5	3	1	1	0	0	0	0	0	0	0	0
9	3	1	1	0	0	0	0	0	0	0	1
11	2	3	3	0	0	0	0	0	0	0	0
29	3	3	1	1	1	1	0	0	0	0	0
15	3	2	3	2	2	0	0	0	0	0	1
17	5	5	6	0	0	0	0	1	0	0	1
Mean	3.2	2.5	2.5	0.5	0.5	0.2	0	0.2	0	0	0.5
Std.Dev.	1.0	1.5	2.0	0.8	0.8	0.4	0	0.4	0	0	0.6
S.E.M.	0.4	0.6	0.8	0.3	0.3	0.2	0	0.2	0	0	0.2

Table 22. Central Venous Pressure (mmHg) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
20	3	3	3	3	3	3	3	3	3	3	3
24	3	3	3	3	3	3	3	3	2	2	2
27	4	4	4	4	4	4	3	4	3	3	3
28	3	3	3	3	3	3	3	3	3	2	2
30	3	3	3	3	3	3	3	2	2	2	2
Mean	3.2	3.2	3.2	3.2	3.2	3.2	3	3	2.6	2.4	2.4
Std.Dev.	0.5	0.5	0.5	0.5	0.5	0.5	0	0.7	0.6	0.6	0.6
S.E.M.	0	0.2	0.2	0.2	0.2	0.2	0	0.4	0.3	0.3	0.3

D. Craniomesenteric Arterial Flow

The craniomesenteric arterial flow (CAF) rates are expressed as a percent of baseline to compensate for size differences among animals, and for variations among animals with respect to vascular anatomy and dominance of the craniomesenteric artery.

On Day 1, immediately after surgery, the ultrasonic flow probe rarely gave a signal due to poor coupling (air between vessel and probe). Due to this fact, most Day 1 data

for craniomesenteric artery flow is unavailable. In four of the animals undergoing shock, however, the probe did couple and gave the data in Table 23 (Figure 8) showing a reduction from baseline to 28±10 percent of baseline at T=6.

Figure 8. Craniomesenteric Arterial Flow of Four Group II and Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

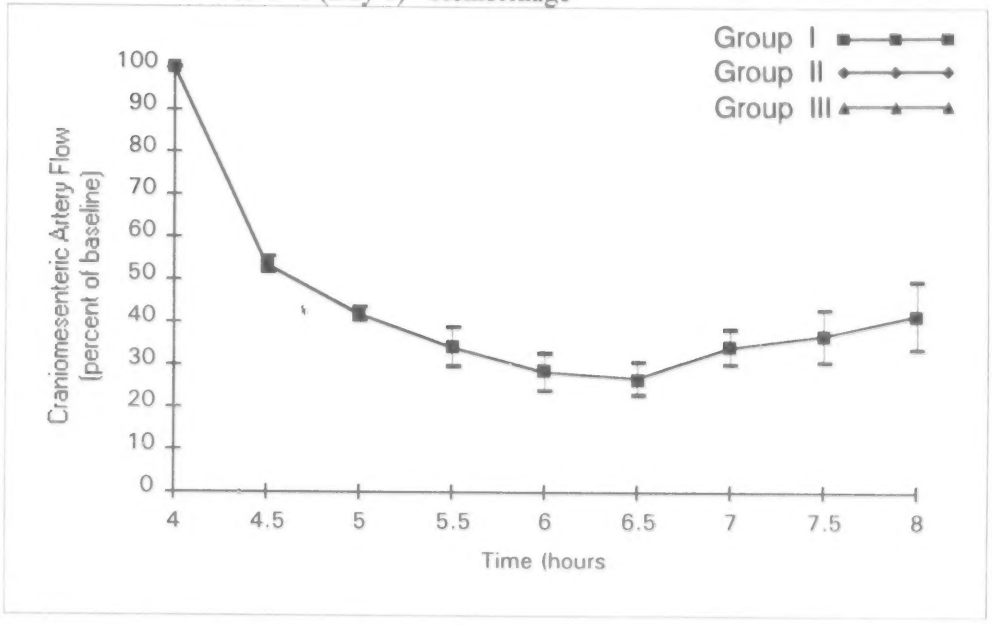


Table 23. Craniomesenteric Arterial Flow (As a percent of baseline) of Group II and Group III Animals from T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
29	100	51.6	43.9	38.1	37.4	34.8	33.6	24.5	24.5
17	100	49.0	37.4	32.3	27.1	30.6	38.9	49.8	55.5
20	100	54.9	42.0	18.5	11.6	13.0	18.5	20.1	19.5
24	100	59.6	40.5	36.1	33.8	28.5	40.7	47.1	58.1
30	100	52.0	46.0	46.0	32.0	27.0	39.0	43.0	51.0
Mean	100	53.4	42.0	34.2	28.4	26.8	34.1	36.9	41.7
Std.Dev.	0	4.0	3.3	10.1	10.1	8.3	9.2	13.7	18.2
S.E.M.	0	1.8	1.5	4.5	4.5	3.7	4.1	6.1	8.2

By Day 3, the flow probe was always coupled and gave useable data as shown in Figure 9. In response to endotoxin, the CAF of the Group I animals (Table 24) quickly fell to 66±11 % at T=48.5, and then recovered to 88±10 % at T=49 where it remained for the remainder of the experimental run. In Group II animals (Table 25), however, a similar fall was seen initially to 55±12 % at T=48.5, but very little recovery was made over the remainder of the four hours. At T=48.5, Group I and Group II were both significantly different from Group III ($p < 0.001$) but not different from each other. At T= 49, Group I and Group III were both significantly different from Group II ($p < 0.001$) but not different from each other. This latter difference also held true at T=52 ($p < 0.001$). The CAF of Group III (Table 24) animals remained quite constant (no statistically significant deviation from baseline on ANOVA).

Figure 9. Craniomesenteric Arterial Flow for T=48 to T=52 (Day 3) - Endotoxin Infusion

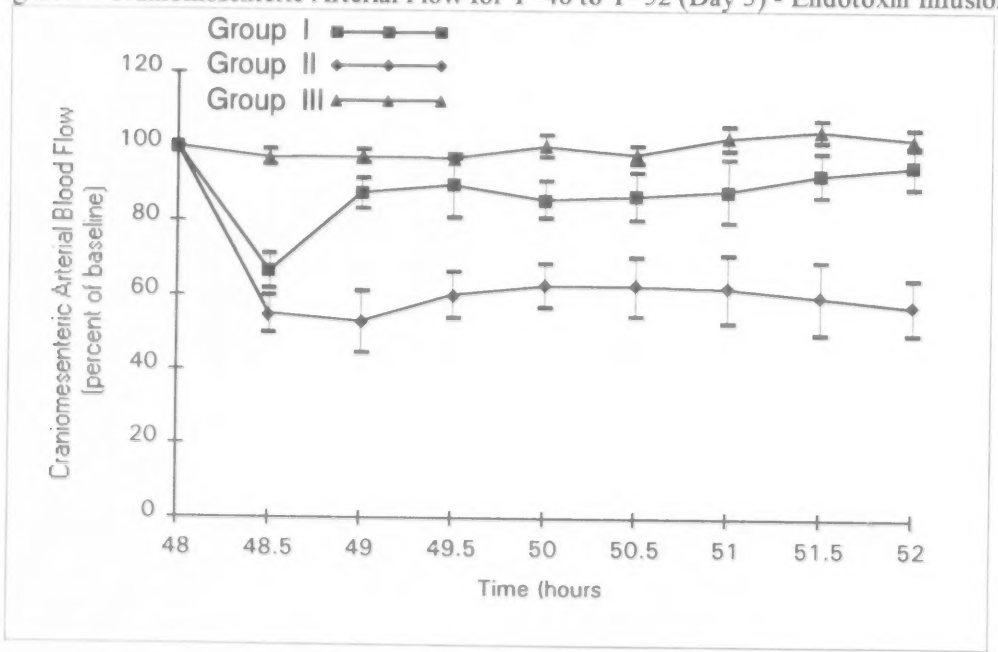


Table 24. Craniomesenteric Arterial Flow (percent of baseline) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	100	71.5	77.8	65.3	70.6	69.9	66.4	77.7	89.9
8	100	51.6	86.6	84.1	93.3	95.1	89.8	102.5	100.8
10	100	67.2	102.0	81.9	84.6	73.8	72.6	81.5	77.2
14	100	72.0	81.3	90.9	81.0	94.9	117.5	108.0	105.5
25	100	54.8	79.9	89.1	80.0	76.2	76.8	79.2	84.4
26	100	81.4	98.9	128.2	107.5	112.3	107.9	108.3	113.0
Mean	100	66.4	87.7	89.9	86.2	87.0	88.5	92.9	95.1
Std.Dev.	0	11.3	10.3	20.9	12.8	16.4	20.5	14.9	13.6
S.E.M.	0	4.6	4.2	8.5	5.2	6.7	8.4	6.1	5.5

Table 25. Craniomesenteric Arterial Flow (percent of baseline) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	100	57.1	89.5	81.6	77.6	86.8	97.4	96.1	86.8
9	100	51.9	56.8	45.2	54.4	46.2	38.3	30.3	35.5
11	100	78.6	50.3	67.4	66.7	73.2	61.3	56.8	61.0
29	100	48.7	51.0	52.6	57.1	45.1	44.0	43.1	44.2
15	100	42.9	41.6	46.3	42.3	44.6	51.2	56.1	53.6
17	100	50.7	29.3	68.5	78.5	80.3	80.5	76.7	63.3
Mean	100	55.0	53.1	60.3	62.8	62.7	62.1	59.8	57.4
Std.Dev.	0	12.5	20.2	14.5	14.2	19.6	22.8	23.6	17.8
S.E.M.	0	5.1	8.3	5.9	5.8	8.0	9.3	9.6	7.3

Table 26. Craniomesenteric Arterial Flow (percent of baseline) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	100	96.6	98.2	97.4	99.2	98.5	95.9	99.1	97.2
24	100	92.2	97.5	97.3	110.5	104.0	109.0	103.5	104.2
27	100	94.8	90.9	97.4	92.9	88.8	99.5	105.8	99.1
28	100	103.6	101.8	96.4	98.2	100.0	98.2	100.0	100.0
30	100	98.8	98.8	97.6	101.2	100.0	111.0	114.6	112.2
Mean	100	97.2	97.5	97.2	100.4	98.3	102.7	104.6	102.5
Std.Dev.	0	4.3	4.0	0.5	6.4	5.7	6.8	6.2	6.0
S.E.M.	0	1.9	1.8	0.2	2.9	2.5	3.0	2.8	2.7

E. Fraction of Inspired Oxygen

The fraction of inspired oxygen (FiO_2) was an experimenter-controlled variable. During hemorrhagic shock and control anaesthetics, it was generally held constant at approximately 50 %. During endotoxic shock, however, we found that in the first hour, it was necessary to increase the FiO_2 considerably in order to maintain PaO_2.

Table 27. Fraction of Inspired Oxygen (percent) for Group I Animals (T=48 to T=52)

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
7	50	50	50	50	50	50	45	45	45	50	50
8	40	40	50	50	90	70	60	60	60	60	70
10	60	60	90	90	90	80	80	70	60	90	90
14	50	70	65	65	60	60	60	65	60	55	55
25	45	45	45	45	60	80	75	60	55	55	50
26	70	70	70	90	70	60	65	65	65	65	65
Mean	52.5	55.8	61.7	65.0	70.0	66.7	64.2	60.8	57.5	62.5	63.3
Std.Dev.	10.8	12.8	16.9	20.5	16.7	12.1	12.4	8.6	6.9	14.4	15.4
S.E.M.	4.43	5.2	6.9	8.4	6.8	4.9	5.1	3.5	2.8	5.9	6.3

Table 28. Fraction of Inspired Oxygen (percent) for Group II Animals (T=48 to T=52)

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
5	40	40	40	40	40	90	90	90	90	90	90
9	90	100	100	100	90	90	70	70	50	50	50
11	80	80	80	80	80	70	50	50	50	50	50
29	55	80	70	70	60	65	65	65	65	65	65
15	50	60	80	80	90	80	80	70	70	70	70
17	70	90	90	90	70	70	75	75	65	65	65
Mean	64.2	75.0	76.67	76.7	71.7	77.5	71.7	70.0	65.0	65.0	65.0
Std.Dev.	19.1	21.7	20.66	20.7	19.4	10.8	13.7	13.0	14.8	14.8	14.8
S.E.M.	7.8	8.9	8.43	8.4	7.9	4.4	5.6	5.3	6.1	6.1	6.1

Table 29. Fraction of Inspired Oxygen (percent) for Group III Animals (T=48 to T=52)

Pig #	Time										
	48	48.25	48.5	48.75	49	49.5	50	50.5	51	51.5	52
20	60	60	60	45	45	45	40	40	40	40	40
24	75	75	75	70	70	60	65	65	70	75	75
27	50	50	50	50	50	50	50	50	50	50	50
28	45	45	45	45	45	45	45	40	40	40	40
30	60	60	60	60	60	60	60	50	40	40	30
Mean	58	58	58	54	54	52	52	49	48	49	47
Std.Dev.	11.5	11.5	11.5	10.8	10.8	7.6	10.4	10.3	13.0	15.2	17.2
S.E.M.	5.2	5.2	5.2	4.9	4.9	3.4	4.6	4.6	5.8	6.8	7.7

F. Animal Weights

The weight of each animal (as recorded on the morning of Day 1) is shown in Table 30. Animals excluded from the study are not shown. The Group I animals had an average weight of 34.75 ± 4.23 kg, the Group II animals 37.67 ± 5.08 kg, and Group III were 37.5 ± 2.37 kg. These differences were not statistically significant ($p > 0.4$).

Table 30. Weights of Experimental Animals (in kilograms)

Group I		Group II		Group III	
Pig #	Weight	Pig #	Weight	Pig #	Weight
7	33	5	38	20	34
8	29.5	9	38	24	40.5
10	37.5	11	30.5	27	37
14	36	29	46	28	38.5
25	31.5	15	35	30	37.5
26	41	17	38.5		
Average	34.8	Average	37.7	Average	37.5
Std. Dev.	4.23	Std. Dev.	5.1	Std. Dev.	2.4

III. Biochemistry

A. Arterial Partial Pressure of Oxygen

Efforts were made to maintain the PaO_2 within the limits of 150 - 200 mmHg at all times by making adjustments to the FiO_2. This proved to be very difficult as the animals' response to hemorrhage and to infusion of endotoxin necessitated frequent adjustments of the FiO_2. As a result, the PaO_2 of animals receiving endotoxin (Groups I and II) was often greater than 200 mmHg early in the experiment. The animals were not allowed to become hypoxic. No significant difference was seen in results of arterial blood gases of the three groups of animals on Day 1 or Day 3 as shown in the following tables.

Table 31. Partial Pressure of Oxygen (mmHg) in Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	384	308	271	219	268	290	231	233	225
26	158	161	155	166	191	200	188	163	153
Mean	271	234.5	213	192.5	229.5	245	209.5	198	189
Std.Dev.	159.8	103.9	82.0	37.5	54.5	63.6	30.4	49.5	50.9
S.E.M.	113	73.5	58	26.5	38.5	45	21.5	35	36

Table 32. Partial Pressure of Oxygen (mmHg) in Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	109	107	106	118	117	118	128	127	136
9	192	208	196	173	120	125	105	115	141
11	160	53	46	205	289	283	312	201	73
29	137	166	195	206	192	145	155	157	170
15	204	150	174	163	158	142	137	212	289
17	110	139	203	239	216	187	192	166	150
Mean	152	137	153	184	182	167	172	163	160
Std.Dev.	40.5	52.9	63.6	42.1	65.4	61.9	74.8	38.7	71.2
S.E.M.	16.5	21.6	26.0	17.2	26.7	25.3	30.5	15.8	29.1

Table 33. Partial Pressure of Oxygen (mmHg) in Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	132	99	165	206	183	229	166	154	149
24	195	171	171	179	153	130	162	89	228
27	165	194	213	210	210	194	183	170	130
28	152	179	180	197	178	173	180	177	177
30	181	161	159	150	353	381	381	114	221
Mean	165	160.8	177.6	188.4	215.4	221.4	214.4	140.8	181
Std.Dev.	25	37	21	25	80	96	93.6	37.9	43.2
S.E.M.	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2

Table 34. Partial Pressure of Oxygen (mmHg) of Arterial Blood in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	173	195	195	210	178	154	118	130	148
8	318	427	388	269	208	131	162	104	131
10	96	243	299	225	327	177	132	110	126
14	166	316	168	152	224	297	269	209	178
25	197	159	131	169	213	182	196	198	205
26	172	267	266	127	203	203	168	149	145
Mean	187.0	267.8	241.2	192.0	225.5	190.7	174.2	150.0	155.5
Std.Dev.	72.7	95.3	95.0	52.3	52.0	57.7	54.0	44.5	30.3
S.E.M.	29.7	38.9	38.8	21.4	21.2	23.5	22.1	18.2	12.4

Table 35. Partial Pressure of Oxygen (mmHg) of Arterial Blood in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	122	219	83	88	139	177	187	130	161
9	389	444	439	403	406	381	382	206	208
11	335	310	354	308	241	157	88	65	77
29	187	282	141	169	172	150	172	172	187
15	164	252	185	221	202	147	215	244	252
17	98	335	175	147	209	246	192	142	129
Mean	215.8	307.0	229.5	222.7	228.2	209.7	206.0	159.8	169.0
Std.Dev.	118.7	78.7	136.9	115.4	93.8	91.7	96.6	62.6	61.4
S.E.M.	48.4	32.1	55.9	47.1	38.3	37.4	39.5	25.5	25.1

Table 36. Partial Pressure of Oxygen (mmHg) in Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	322	300	256	237	212	209	227	246	219
24	190	210	213	145	173	169	147	197	178
27	199	173	187	187	196	200	183	199	173
28	208	203	204	182	210	186	190	188	179
30	176	176	169	175	188	209	196	174	192
Mean	219	212.4	205.8	185.2	195.8	194.6	188.6	200.8	188.2
Std.Dev.	58.8	51.6	32.7	33.2	16.2	17.1	28.7	27.1	18.6
S.E.M.	26.3	23.1	14.6	14.9	7.2	7.7	12.8	12.1	8.3

B. Arterial Partial Pressure of Carbon Dioxide

Efforts were made to maintain the $PaCO_2$ within the limits of 40 ± 2 mmHg at all times by making adjustments to the ventilator rate and tidal volume. This proved to be very difficult as the animals' response to hemorrhage and to infusion of endotoxin necessitated frequent adjustments of these parameters. As a result, the $PaCO_2$ of the animals often strayed slightly beyond the prescribed limits. The mean $PaCO_2$ of the

groups, however, was generally maintained within the parameters and the animals were not allowed to become extremely hypo- or hypercarbic. No significant difference was seen in results of arterial blood gases of the three groups of animals as shown in Tables 37, 38 and 39.

Table 37. Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	39.1	39.7	39.9	36.8	43	38.8	38.6	40.1	45.2
26	38.9	39.5	41.8	42.3	37.1	38.2	36.4	42.2	40.9
Mean	39	39.6	40.9	39.6	40.1	38.5	37.5	41.2	43.1
Std.Dev.	0.1	0.1	1.3	3.9	4.2	0.4	1.6	1.5	3.0
S.E.M.	0.1	0.1	1.0	2.8	3.0	0.3	1.1	1.1	2.2

Table 38. Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	45.1	45.4	41.3	43.8	42.7	43.6	42.2	40.5	40.4
9	38.7	37.9	35.4	34.3	35.1	37.6	37.9	30.1	30.9
11	39.7	37.7	34.6	36.3	39.2	39.8	43.2	48.3	47.1
29	41.5	42	38.4	40	40	36.7	36.9	32.9	37.9
15	41.9	40.9	42.2	38.1	39.9	40.7	38.6	48.5	47.4
17	40.3	36.9	39.4	39.8	40.1	39.6	42.5	42.8	40.7
Mean	41.2	40.1	38.6	38.7	39.5	39.7	40.2	40.5	40.7
Std.Dev.	2.2	3.3	3.1	3.3	2.5	2.4	2.7	7.7	6.2
S.E.M.	0.9	1.3	1.3	1.3	1.0	1.0	1.1	3.1	2.5

Table 39. Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	40.3	33.7	41.4	41.5	39.6	40.2	45	46.5	53
24	41.1	35.7	37.8	40.5	35.9	37.2	37	35.7	27.9
27	42.9	37	36.1	35.4	37.9	34	30.3	31	31.6
28	39.1	34.2	35.3	37.6	43.2	38.2	40.3	40.6	38.4
30	41.9	34.5	33.6	34.4	37.4	32.4	36.1	40.5	41.8
Mean	41.1	35.0	36.8	37.9	38.8	36.4	37.7	38.9	38.5
Std.Dev.	1.5	1.3	3.0	3.1	2.8	3.2	5.4	5.8	9.8
S.E.M.	0.7	0.6	1.3	1.4	1.2	1.4	2.4	2.6	4.4

Table 40. Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	41.7	43.4	32.1	38.4	41.3	44	36.9	33.7	24
8	41.7	38.8	43	43.5	41.4	44.3	43.4	47.2	40
10	38	38.9	39.9	42.7	40.8	42.4	43.3	39	41.6
14	43.7	40.4	40.2	39.3	39	47	49.9	38.4	38.8
25	39.3	47.3	41.5	39.5	38.6	43.8	41.5	41.8	41.5
26	40.8	40.7	40.1	42.2	43	45.3	44.5	43.5	42
Mean	40.9	41.6	39.5	40.9	40.7	44.5	43.3	40.6	38.0
Std.Dev.	2.0	3.3	3.8	2.1	1.6	1.6	4.2	4.7	7.0
S.E.M.	0.8	1.3	1.6	0.9	0.7	0.6	1.7	1.9	2.8

Table 41. Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	41.2	51.6	43.5	41.8	43.3	47.3	47.3	45.3	45.6
9	40.2	39.2	41.3	43.5	44.3	42.5	41.7	41	40
11	38.6	44	40	41.8	43.1	43	43.2	39.8	41.6
29	39.1	42.1	43.5	43.4	41	44.2	40.1	40.5	40.3
15	42.4	47	39.8	43.6	52.6	51.8	58	60	57
17	39.8	38.9	42.9	41.1	42.5	43.4	45.5	38.5	37.6
Mean	40.2	43.8	41.8	42.5	44.5	45.4	46.0	44.2	43.7
Std.Dev.	1.4	4.9	1.7	1.1	4.1	3.6	6.4	8.1	7.0
S.E.M.	0.6	2.0	0.7	0.5	1.7	1.5	2.6	3.3	2.9

Table 42. Partial Pressure of Carbon Dioxide (mmHg) in Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

	Time								
Pig #	48	48.5	49	49.5	50	50.5	51	51.5	52
20	47.8	44.1	43.8	44.5	43.8	43.6	42.2	44.5	45.7
24	39.9	39.6	38.2	38.9	40.2	39.2	41.4	38.5	40.8
27	41.5	40.2	38.1	40.1	41.1	35.4	40.2	38.8	37.7
28	39.6	40.4	43.5	39.5	38	41.5	40.2	40.6	39.3
30	39.6	45.2	46.4	46.1	42.1	43	41.5	41.9	40.2
Mean	42.7	43.0	43.2	43.1	42.5	42.2	42.8	42.6	42.6
Std.Dev.	4.1	3.5	4.4	4.2	4.1	5.0	4.1	4.9	5.3
S.E.M.	1.8	1.6	2.0	1.9	1.9	2.3	1.8	2.2	2.4

C. Arterial Hydrogen Ion Concentration

Despite slight fluctuations in the hydrogen ion concentration ([H+]), no statistically significant trends were noted. On Day 1, the Group II animals (Table 44) and Group III animals (Table 45) demonstrated trends toward developing mild acidosis during the hemorrhagic shock. The Group I (Table 46) and Group II (Table 47) animals demonstrated a similar trend during endotoxic shock.

Table 43. Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	41.6	44	44.5	46	46.2	46.2	44.3	44.8	44.3
26	32.7	33.8	35.2	35.2	33	33.1	32.1	36	35.3
Mean	37.2	38.9	39.9	40.6	39.6	39.7	38.2	40.4	39.8
Std.Dev.	6.3	7.2	6.6	7.6	9.3	9.3	8.6	6.2	6.4
S.E.M.	4.5	5.1	4.7	5.4	6.6	6.6	6.1	4.4	4.5

Table 44. Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	39.7	38.9	39.9	41.8	44.1	45.2	46.5	48.9	54
9	32.6	31.6	31.6	31.6	34.8	40.2	39.9	35.9	38.2
11	30.7	29.0	27.7	30.2	31.5	31.8	35.4	38	36.4
29	38.9	36	35.7	36.6	37.6	38.7	39	37.2	44.9
15	35.1	35	35.6	34.1	34.8	36.3	33.8	45.1	42.2
17	32.6	31	33.6	36.3	38	40.5	43	43.5	40.3
Mean	34.9	33.6	34.0	35.1	36.8	38.8	39.6	41.4	42.7
Std.Dev.	3.7	3.7	4.1	4.1	4.3	4.5	4.7	5.2	6.3
S.E.M.	1.5	1.5	1.7	1.7	1.8	1.8	1.9	2.1	2.6

Table 45. Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	38.9	35.3	44.2	48	54.3	52.5	64.4	68.2	73.8
24	33.4	30.5	31.3	32.8	30	32.7	34.3	34.4	31.7
27	34.8	31.7	33.7	32.1	36	35.1	32.8	40.1	43
28	33.10	30.9	31.4	33.8	36.7	35.8	37.3	36.4	35.3
30	35	30.6	30.4	32	36.4	35.9	41.6	45.9	48.5
Mean	35.0	31.8	34.2	35.7	38.7	38.4	42.1	45.0	46.5
Std.Dev.	2.3	2.0	5.7	6.9	9.2	8.0	12.9	13.7	16.6
S.E.M.	1.0	0.9	2.6	3.1	4.1	3.6	5.8	6.1	7.4

Table 46. Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	34	35.6	30.1	35.6	39.7	40.2	35.3	34.5	36.1
8	33.3	33.2	35.3	34.8	33.7	34.8	33.7	37.9	32.7
10	30.1	33.2	34.2	36.3	34.	36.2	37.2	39.5	42.7
14	34.2	29.9	30.3	32.1	33.3	38.5	38.6	32.3	30.4
25	36	42.2	41	37.1	36.5	41.3	41.4	41	40
26	36.1	36.6	37.2	37.8	37.9	40.1	39.7	37.9	39.3
Mean	34.0	35.1	34.7	35.6	35.9	38.5	37.7	37.2	36.9
S.D.	2.2	4.2	4.2	2.0	2.5	2.5	2.9	3.2	4.7
S.E.M.	0.9	1.7	1.7	0.8	1.0	1.0	1.2	1.3	1.9

Table 47. Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	37.8	44.9	42.6	41.4	44	47.3	46.7	43.6	43.3
9	32.4	31.8	34.3	36.2	36.6	35.1	34.9	35.8	36.6
11	27.7	34.8	34.2	33.7	36.1	36.8	36.2	34.3	34.7
29	32.2	35	37.8	36.5	35.2	36.1	32.5	31.8	33.2
15	34.1	43.7	42.1	42.4	45.7	44.3	48.2	50.2	46.6
17	30.3	29.9	35	33.7	34.3	34.9	34.7	29.4	30.1
Mean	32.4	36.7	37.7	37.3	38.7	39.1	38.9	37.5	37.4
Std.Dev.	3.4	6.2	3.9	3.8	4.9	5.3	6.8	7.9	6.3
S.E.M.	1.4	2.5	1.6	1.5	2.0	2.2	2.8	3.2	2.6

Table 48. Hydrogen Ion Concentration (nmol/l) in Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	40.1	37.2	37	36.3	37.5	36.9	35.6	37.3	37
24	32.7	31.3	31.2	31.3	32.1	31.5	33.7	31.3	32.5
27	34.4	33.4	31.2	33.3	33	29.4	31.2	31.1	31
28	34.1	34.4	35.6	32.1	33.2	34.8	33.5	34.2	31.8
30	28.8	30.8	33.7	33	36.5	38.9	40	39.6	37.9
Mean	34.0	33.4	33.7	33.2	34.5	34.3	34.8	34.7	34.0
Std.Dev.	4.1	2.6	2.6	1.9	2.4	3.9	3.3	3.7	3.1
S.E.M.	1.8	1.2	1.2	0.9	1.1	1.7	1.5	1.7	1.4

D. Arterial Bicarbonate Concentration

During hemorrhagic shock, Group II animals (Table 50) and Group III animals (Table 51) both demonstrated a steady loss of bicarbonate relative to the Group I controls (Table 49) over the four hours. This did not, however, reach statistical significance.

Table 49. Arterial Bicarbonate (nmol/l) of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	41.6	44	44.5	46	46.2	46.2	44.3	44.8	44.3
26	32.7	33.8	35.2	35.2	33	33.1	32.1	36	35.3
Mean	37.2	38.9	39.9	40.6	39.6	39.7	38.2	40.4	39.8
Std.Dev.	6.3	7.2	6.6	7.6	9.3	9.3	8.6	6.2	6.4
S.E.M.	4.5	5.1	4.7	5.4	6.6	6.6	6.1	4.4	4.5

Table 50. Arterial Bicarbonate (nmol/l) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	28.3	29.1	25.8	26.1	24.2	24	22.6	20.7	18.7
9	29.6	30	27.9	27	25.1	23.3	23.7	20.9	20.2
11	32.2	32.5	31.1	29.9	31	31.2	30.4	31.7	32.2
29	28.5	28.2	27.5	27.4	27.5	25.3	23.70	23.9	23.2
15	29.8	29.1	29.6	27.8	28.5	27.9	28.5	26.8	28
17	30.2	29.6	29.3	27.3	26.3	24.4	24.6	24.5	25.2
Mean	29.8	29.8	28.5	27.6	27.1	26.0	25.6	24.8	24.6
Std.Dev.	1.4	1.5	1.9	1.3	2.5	3.0	3.1	4.1	5.0
S.E.M.	0.6	0.6	0.8	0.5	1.0	1.2	1.3	1.7	2.1

Table 51. Arterial Bicarbonate (nmol/l) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	25.9	23.8	23.3	21.6	18.2	19.1	17.4	17	17.9
24	30.6	29.1	30.1	30.8	29.8	28.4	26.9	25.8	22
27	30.7	29.1	26.6	27.5	26.3	24.1	21.6	19.3	18.3
28	29.4	27.6	27.9	27.7	29.3	26.6	26.9	27.8	27.0
30	29.9	28.1	27.6	26.8	25.6	22.5	21.6	22	21.5
Mean	29.3	27.5	27.1	26.9	25.8	24.1	22.9	22.4	21.3
Std.Dev.	2.0	2.2	2.5	3.3	4.6	3.6	4.1	4.5	3.7
S.E.M.	0.9	1.0	1.1	1.5	2.1	1.6	1.8	2.0	1.6

During endotoxic shock, both Group I animals (Table 52) and Group II animals (Table 53) showed a small decline in bicarbonate levels as compared to Group III (Table 54) but at T=52, only the difference between Group I and Group III reacheed statistical significance ($p < 0.05$).

Table 52. Arterial Bicarbonate (nmol/l) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	30.5	30.3	26.6	26.8	25.9	27.3	26.1	24.5	16.6
8	31.1	29.1	30.3	31.2	30.6	31.7	32	31	30.4
10	31.5	29.2	29.1	29.3	29.4	29.2	29	24.6	24.3
14	31.9	33.7	33.1	30.5	29.3	30.4	32.1	29.6	31.8
25	27.2	27.9	25.2	26.5	26.4	26.4	25	25.4	26
26	28.1	27.7	26.9	27.9	28.2	28.2	27.9	28.5	26.7
Mean	30.1	29.7	28.5	28.7	28.3	28.9	28.7	27.3	26.0
Std.Dev.	1.9	2.2	2.9	2.0	1.8	2.0	3.0	2.8	5.4
S.E.M.	0.8	0.9	1.2	0.8	0.8	0.8	1.2	1.1	2.2

Table 53. Arterial Bicarbonate (nmol/l) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	28.6	25.5	25.7	25.2	24.5	24.9	25.3	25.9	26.2
9	30.9	30.7	30	29.9	30.1	30.2	29.7	28.5	27.2
11	34.7	31.5	29.2	31	29.8	29.1	29.7	29	29.9
29	30.2	30	28.7	29.6	29	30.5	30.8	31.6	30.3
15	30.9	24.7	23.6	25.6	28.7	29.2	29.9	29.7	30.5
17	32.7	32.4	31.1	30.3	30.9	31	32.7	32.6	31.1
Mean	31.3	29.1	28.1	28.6	28.8	29.2	29.7	29.6	29.2
Std.Dev.	2.1	3.2	2.8	2.5	2.3	2.2	2.4	2.4	2.0
S.E.M.	0.9	1.3	1.2	1.0	0.9	0.9	1.0	1.0	0.8

Table 54. Arterial Bicarbonate (nmol/l) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	29.7	29.5	29.5	30.5	29.1	29.4	29.6	29.7	30.8
24	30.4	31.6	30.5	30.9	31.2	31	30.6	30.6	31.2
27	30.1	30	30.5	30	31	29.9	32.2	31	30.2
28	28.9	29.2	30.4	30.6	28.6	29.8	29.9	29.6	30.7
30	34.2	36.6	34.4	34.8	36.5	35.6	36.2	35.3	34.9
Mean	30.7	31.4	31.1	31.4	31.3	31.1	31.7	31.2	31.6
Std.Dev.	2.1	3.1	1.9	2.0	3.1	2.6	2.7	2.4	1.9
S.E.M.	0.9	1.4	0.9	0.9	1.4	1.2	1.2	1.1	0.9

E. Arterial Oxygen Saturation

With very few exceptions, arterial oxygen saturation was maintained at levels greater than 99% during both hemorrhagic and endotoxic shocks.

Table 55. Oxygen Saturation (percent) of Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	99.9	99.9	99.8	99.7	99.8	99.9	99.8	99.8	99.7
26	99.5	99.5	99.4	99.5	99.7	99.8	99.7	99.5	99.4
Mean	99.7	99.7	99.6	99.6	99.8	99.9	99.8	99.7	99.6
Std.Dev.	0.3	0.3	0.3	0.1	0.1	0.1	0.1	0.2	0.2
S.E.M.	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.2	0.2

Table 56. Oxygen Saturation (percent) of Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	98.2	98.2	98.1	98.5	98.4	98.4	98.7	98.5	98.7
9	99.7	99.8	99.8	99.7	98.9	98.8	98.1	98.7	99.3
11	99.6	91	87.8	99.8	99.9	99.9	99.9	99.7	94.9
29	98.7	99.5	99.7	99.7	99.7	99.3	99.4	99.5	99.5
15	99.8	99.4	99.6	99.6	99.5	99.3	99.3	99.7	99.9
17	98.6	99.4	99.8	99.8	99.8	99.6	99.6	99.4	99.3
Mean	99.1	97.9	97.5	99.5	99.4	99.2	99.2	99.3	98.6
Std.Dev.	0.7	3.4	4.8	0.5	0.6	0.5	0.7	0.5	1.9
S.E.M.	0.3	1.4	2.0	0.2	0.2	0.2	0.3	0.2	0.8

Table 57. Oxygen Saturation (percent) of Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	99	98.1	99.4	99.7	99.4	99.7	99.1	98.7	98.4
24	99.7	99.7	99.6	99.7	99.5	99.2	99.5	97.4	99.9
27	99.5	99.8	99.8	99.8	99.8	99.7	99.7	99.5	98.9
28	99.5	99.7	99.7	99.7	99.6	99.6	99.6	99.6	99.6
30	99.6	99.6	99.6	99.5	99.9	100.0	99.9	98.1	99.7
Mean	99.5	99.4	99.6	99.7	99.6	99.6	99.6	98.7	99.3
Std.Dev.	0.3	0.7	0.2	0.1	0.2	0.3	0.3	0.9	0.6
S.E.M.	0.1	0.3	0.1	0.1	0.1	0.1	0.1	0.4	0.3

Table 58. Oxygen Saturation (percent) of Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	99.6	99.7	99.8	99.8	99.6	99.3	98.8	99.2	99.4
8	99.9	100	100	99.9	99.8	99.1	99.3	98	99.2
10	98.2	99.9	99.9	99.8	99.9	99.6	98.8	98.3	98.7
14	99.6	99.9	99.6	99.5	99.8	99.9	99.9	99.8	99.7
25	99.7	99.3	98.9	99.6	99.8	99.6	99.7	99.7	99.7
26	99.6	99.9	99.9	98.9	99.7	99.7	99.5	99.3	99.2
Mean	99.4	99.8	99.7	99.6	99.8	99.5	99.3	99.1	99.3
Std.Dev.	0.6	0.3	0.4	0.4	0.1	0.3	0.5	0.7	0.4
S.E.M.	0.3	0.1	0.2	0.2	0.04	0.1	0.2	0.3	0.2

Table 59. Oxygen Saturation (percent) of Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	98.8	99.7	95.8	96.6	99	99.5	99.5	98.8	99.4
9	100	100	100	100	100	100	100	99.8	99.8
11	100	99.9	99.9	99.9	99.8	99.4	97	93.5	95.8
29	99.7	99.9	99.2	99.6	99.6	99.4	99.6	99.6	99.7
15	99.5	99.3	99.6	99.8	99.6	99.1	99.7	99.8	99.8
17	98.2	99.9	99.6	99.4	99.8	99.9	99.7	99.4	99.2
Mean	99.4	99.8	99.0	99.2	99.6	99.6	99.3	98.5	99.0
Std.Dev.	0.7	0.3	1.6	1.3	0.3	0.3	1.1	2.5	1.6
S.E.M.	0.3	0.1	0.7	0.5	0.1	0.1	0.5	1.0	0.6

Table 60. Oxygen Saturation (percent) of Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	99.9	99.9	99.9	99.8	99.8	99.8	99.8	99.8	99.8
24	99.7	99.8	99.8	99.4	99.6	99.6	99.4	99.8	99.7
27	99.7	99.6	99.7	99.7	99.7	99.8	99.7	99.8	99.7
28	99.8	99.8	99.7	99.7	99.8	99.7	99.7	99.7	99.7
30	99.7	99.7	99.6	99.6	99.7	99.9	99.8	99.7	99.8
Mean	99.8	99.8	99.7	99.6	99.7	99.8	99.7	99.8	99.7
Std.Dev.	0.1	0.1	0.1	0.2	0.1	0.1	0.2	0.1	0.1
S.E.M.	0.04	0.05	0.05	0.07	0.04	0.05	0.07	0.02	0.02

F. Portal Venous Partial Pressure of Oxygen

Due to sampling error, accurate representative values for the Group I animals on Day 1 were not available. Comparison might be made with controls (Group III) from Day 3. A significant fall in PpO_2 was noted during the hemorrhagic shock in Group II animals (Table 61) and in Group III (Table 62). This was not observed during endotoxic shock

(Day 3). There was no significant difference in PpO_2 among the three groups (Tables 63, 64, and 65) on Day 3.

Figure 10. Partial Pressure of Oxygen in Portal Venous Blood for T=4 to T=8 (Day 1) - Hemorrhage

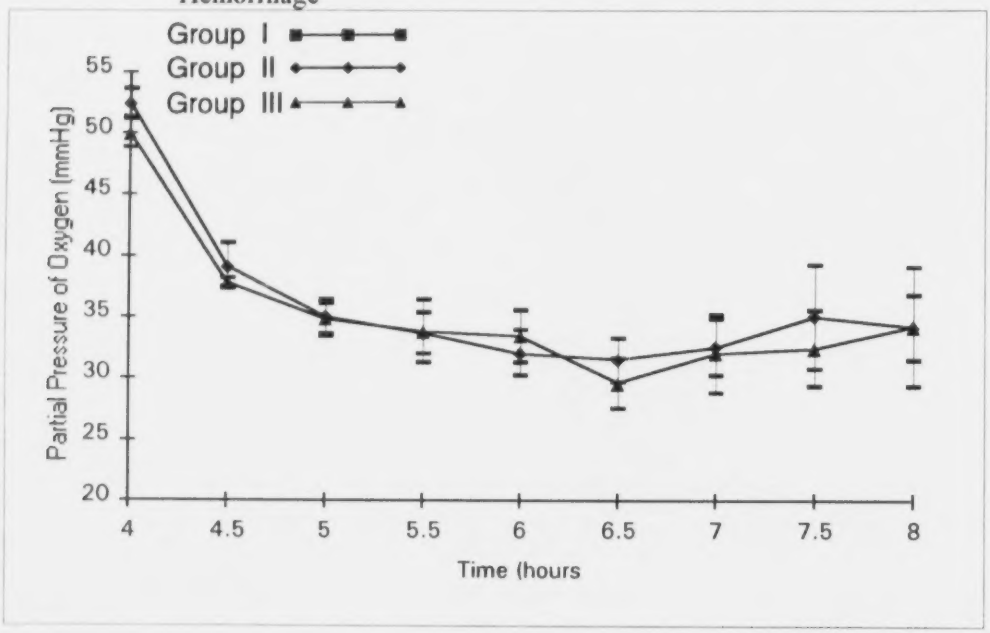


Table 61. Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	51	47	37	29	29	27	28	27	30
9	57	42	40	36	31	28	27	25	25
11	51	35	30	39	40	37	43	44	41
29	53	37	36	34	34	31	32	30	33
15	54	37	33	35	31	37	33	51	42
17	49	37	34	29	27	29	32	33	34
Mean	52.5	39.2	35.0	33.7	32.0	31.5	32.5	35.0	34.2
Std.Dev.	2.8	4.5	3.5	4.0	4.6	4.5	5.7	10.3	6.5
S.E.M.	1.2	1.8	1.4	1.6	1.9	1.8	2.3	4.2	2.7

Table 62. Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	51	38	39	30	36	30	35	35	39
24	53	38	34	38	33	26	25	26	22
27	48	39	31	27	27	25	24	24	23
28	47	37	36	41	40	36	40	40	41
30	51	37	34	33	31	31	36	37	46
Mean	50	37.8	34.8	33.8	33.4	29.6	32	32.4	34.2
Std.Dev.	2.5	0.8	3.0	5.7	4.9	4.4	7.1	7.0	11.0
S.E.M.	1.1	0.4	1.3	2.6	2.2	2.0	3.2	3.1	4.9

Figure 11. Partial Pressure of Oxygen in Portal Venous Blood for T=48 to T=52 (Day 3) - Endotoxin Infusion

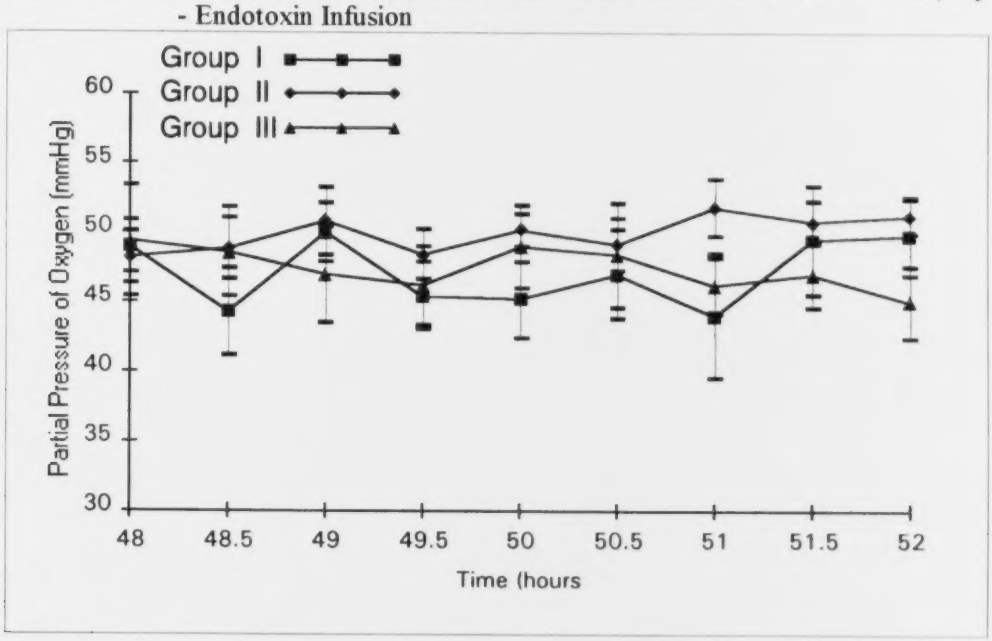


Table 63. Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	50	NA	NA	38	44	43	38	NA	53
8	49	44	55	48	45	44	35	46	48
14	55	54	53	52	55	59	60	61	58
25	48	38	45	47	44	48	47	51	49
26	43	41	47	42	38	41	40	40	41
Mean	49	44.3	50	45.4	45.2	47	44	49.5	49.8
Std.Dev.	4.3	7.0	4.8	5.5	6.1	7.2	10.0	8.9	6.3
S.E.M.	1.9	3.1	2.1	2.4	2.8	3.2	4.5	4.0	2.8

Table 64. Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	47	47	46	42	49	55	58	53	54
9	49	43	47	48	51	47	45	45	48
11	NA	49	50	NA	NA	47	50	NA	NA
29	46	45	55	50	52	48	49	51	51
15	55	54	47	49	46	44	54	54	54
17	44	55	60	53	53	54	55	51	49
Mean	48.2	48.8	50.8	48.4	50.2	49.2	51.8	50.8	51.2
Std.Dev.	4.2	4.8	5.6	4.0	2.8	4.4	4.7	3.5	2.8
S.E.M.	1.9	2.2	2.5	1.8	1.2	2.0	2.1	1.6	1.2

Table 65. Partial Pressure of Oxygen (mmHg) in Portal Venous Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	65	58	59	57	58	60	52	56	54
24	48	54	45	40	44	41	42	45	39
27	43	41	38	44	44	42	44	43	41
28	48	46	45	44	45	44	43	43	45
30	43	44	48	46	54	55	50	48	46
Mean	49.4	48.6	47.0	46.2	49.0	48.4	46.2	47.0	45.0
Std.Dev.	9.1	7.1	7.7	6.4	6.6	8.6	4.5	5.4	5.8
S.E.M.	4.1	3.2	3.4	2.9	2.9	3.8	2.0	2.4	2.6

G. Portal Venous Hydrogen Ion Concentration

On Day 1, hemorrhage causeed portal acidosis (Figure 12) with an elevation of hydrogen ion in Group II animals (Table 67) from 38±3 nmol/l at T=4 to 54±10 nmol/l at T=8, and from 39±3 nmol/l at T=4 to 63±22 nmol/l at T=8 in Group III (Table 68). These changes did not, however, reach statistical significance. Group I animals (Table 66) showed no significant deviation from their baseline level over the four hours.

Figure 12. Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood for T=4 to T=8 (Day 1) - Hemorrhage

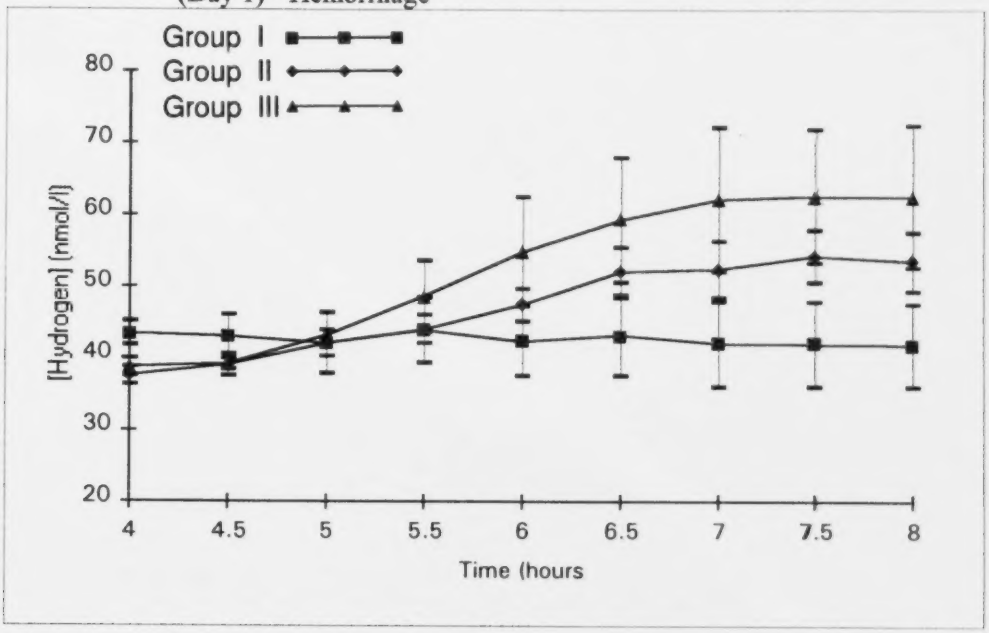


Table 66. Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	45	45.9	46.2	48.5	47.2	48.8	48	47.8	47.5
26	41.8	40.1	37.8	39.2	37.4	37.5	36.1	36.1	36.1
Mean	43.4	43.0	42.0	43.9	42.3	43.2	42.1	42.0	41.8
Std.Dev.	2.3	4.1	5.9	6.6	6.9	8.0	8.4	8.3	8.1
S.E.M.	1.6	2.9	4.2	4.7	4.9	5.7	6.0	5.9	5.7

Table 67. Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	40.4	40.4	47.2	50.6	55.3	60.7	65	70	66.5
9	35.2	37.8	40.4	40.6	46.2	54.5	52.7	51.9	51.5
11	35.1	35.1	34.7	37.8	41.2	43.7	43.1	45.3	40.5
29	41.6	45.6	46.8	48.1	49.8	60.1	62.1	57.8	65.2
15	36.9	39.9	43.0	41.4	42.3	40.5	40.1	50.1	50.0
17	36	35.5	40.3	45	49.8	52.7	51.9	50.6	47.4
Mean	37.5	39.1	42.1	43.9	47.4	52.0	52.5	54.3	53.5
Std.Dev.	2.8	3.9	4.7	4.9	5.3	8.4	9.9	8.7	10.3
S.E.M.	1.1	1.6	1.9	2.0	2.2	3.4	4.1	3.5	4.2

Table 68. Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	42.2	42	55.3	68.2	83.4	91.6	100	95.5	97.1
24	37.2	37.3	40.6	41.3	39.7	43.5	47.3	45.8	43.8
27	37.3	39.1	41.6	48.5	54.7	57.5	61.8	68.2	69.8
28	36.5	38.5	39.5	44.4	44.6	45	44.4	43.8	43.9
30	40.4	38.9	38.9	40.6	51.6	58.9	57.2	59.6	58.1
Mean	38.7	39.2	43.2	48.6	54.8	59.3	62.1	62.6	62.5
Std.Dev.	2.5	1.7	6.9	11.4	17.0	19.4	22.3	21.0	22.2
S.E.M.	1.1	0.8	3.1	5.1	7.6	8.7	10.0	9.4	9.9

Over the four hours of experimentation on Day 3, Group I (Table 69) and Group II (Table 70) animals, who received endotoxin, displayed an elevation of portal hydrogen ion concentration from 38±3 nmol/l at T=48 to 44±3 nmol/l at T=50.5, and 37±5 nmol/l at T=48 to 44±9 nmol/l at T=50.5 respectively (not statistically significant). The control animals of Group III (Table 71) showed very little deviation from their baseline value of 38±5 nmol/l. There was no significant difference between the groups.

Figure 13. Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood for T=48 to T=52 (Day 3) - Endotoxin Infusion

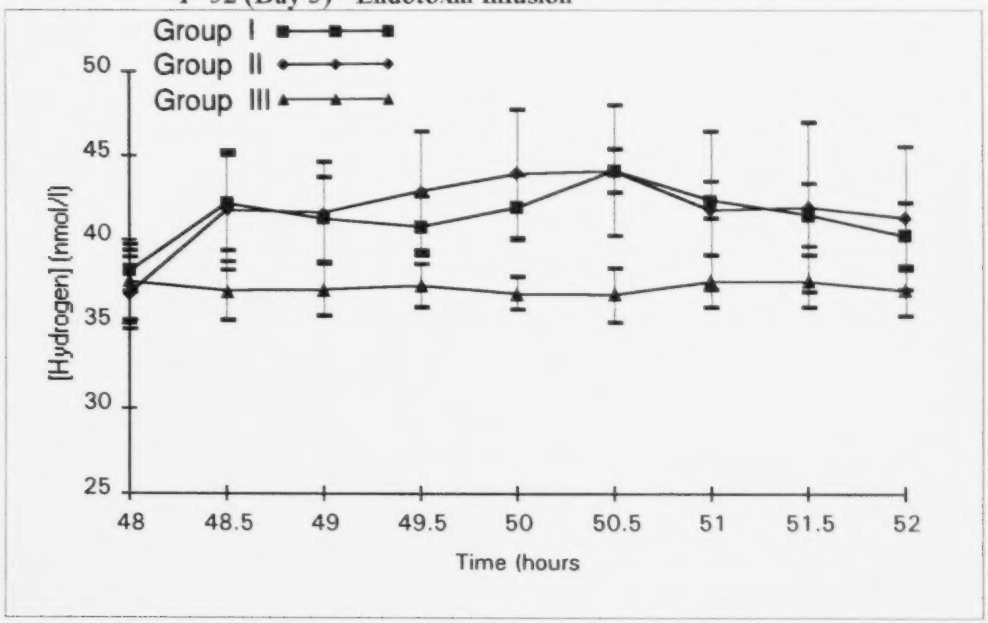


Table 69. Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	37.3	NA	NA	39.6	45.6	44.8	41.4	NA	41.2
8	41.2	44.9	44.9	44.4	41	40.5	39.7	43.7	40.6
14	34.1	32.9	33.2	34.8	35.6	42.3	40.7	35.3	32.6
25	38	47.3	45.4	41.2	41.6	44.7	44.4	42.6	43.5
26	40.3	43.6	41.5	44	45.9	48.4	45.6	44.3	43.2
Mean	38.2	42.2	41.3	40.8	41.9	44.1	42.4	41.5	40.2
Std.Dev.	2.8	6.4	5.6	3.9	4.2	3.0	2.5	4.2	4.4
S.E.M.	1.3	2.9	2.5	1.7	1.9	1.3	1.1	1.9	2.0

Table 70. Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	44.5	52.5	48.6	51.3	52.6	56.6	54.7	50	48.8
9	33.7	37.1	36.6	36.7	35.6	36.1	34.2	36.7	36.3
11	NA	36.2	39.4	NA	NA	41.8	33.1	NA	NA
29	35.1	41.4	38.3	39.4	39	38	35.2	34.8	34.7
15	37.9	50	51.3	51.4	53.7	53.1	55.7	57.3	54
17	33	33.4	35.5	35.7	38.8	39.1	37.7	30.8	32.7
Mean	36.8	41.8	41.6	42.9	43.9	44.1	41.8	41.9	41.3
Std.Dev.	4.7	7.8	6.7	7.8	8.5	8.6	10.5	11.2	9.5
S.E.M.	2.1	3.5	3.0	3.5	3.8	3.8	4.7	5.0	4.2

Table 71. Hydrogen Ion Concentration (nmol/l) in Portal Venous Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	43.7	41.7	40.6	40	39.3	39.7	39.8	40.8	39.4
24	33.3	32.6	32.9	34.6	34	32.4	33.7	34	33.9
27	39.7	37.8	35.9	35.9	35.2	33.4	34.4	34	33.1
28	39.3	39.5	40.4	40.8	38.1	38.9	38.3	37.8	39.1
30	31.6	33.3	35.5	35.1	37.5	39.4	41.5	41	39.5
Mean	37.5	37.0	37.1	37.3	36.8	36.8	37.5	37.5	37.0
Std.Dev.	5.0	3.9	3.4	2.9	2.2	3.6	3.4	3.5	3.2
S.E.M.	2.2	1.8	1.5	1.3	1.0	1.6	1.5	1.5	1.4

H. Portal Venous Oxygen Saturation

The oxygen saturation of portal venous blood (SaO_2) shows a significant decline ($p < 0.05$) in animals undergoing hemorrhagic shock (Table 73, Table 74) while control animals (Table 72) maintain a constant SpO_2 during anaesthetic. Group II animals fall from a mean of 87±2 % at T=4 to 54±16 % at T=8, and Group III animals fall from 85±1 % at T=4 to 50±22 % at T=8, while control animals from Group I remain within 3 % of their baseline of 93±1 %. These relationships are depicted graphically in Figure 14.

Figure 14. Oxygen Saturation (percent) of Portal Venous Blood for T=4 to T=8 - Hemorrhage

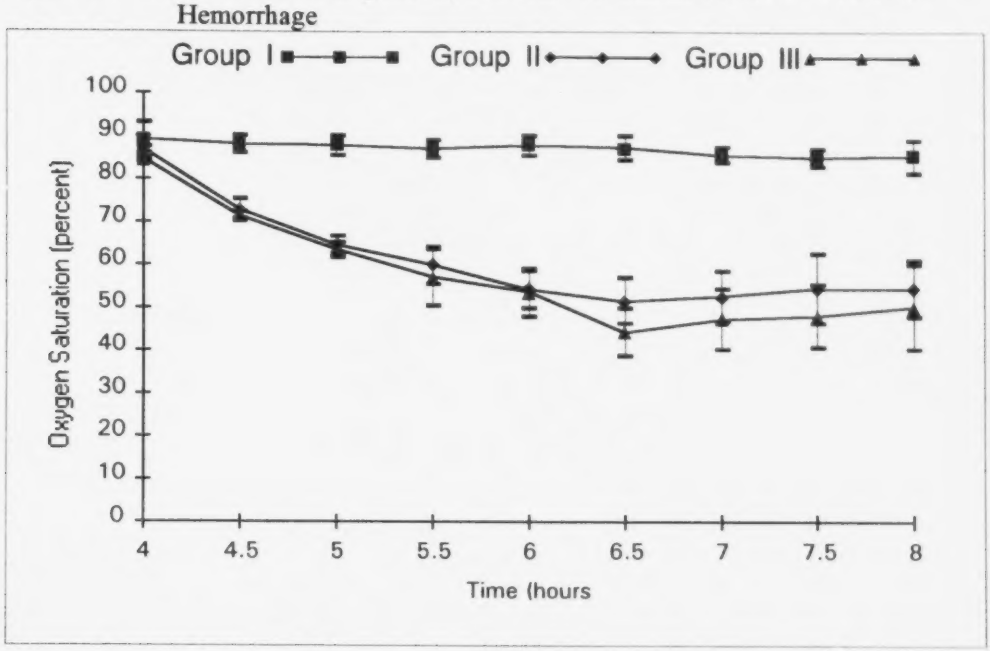


Table 72. Oxygen Saturation (percent) of Portal Venous Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	93.2	90.1	90.1	89.3	90.3	90	87.4	87.1	89.2
26	85	86.1	85.6	84.9	85.5	84.6	83.8	82.9	81.7
Mean	89.1	88.1	87.9	87.1	87.9	87.3	85.6	85	85.5
Std.Dev.	5.8	2.8	3.2	3.1	3.4	3.8	2.6	3.0	5.3
S.E.M.	4.1	2.0	2.3	2.2	2.4	2.7	1.8	2.1	3.8

Table 73. Oxygen Saturation (percent) of Portal Venous Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	85.3	82.3	64.8	46.6	44	38.2	37.8	34.2	36.9
9	90.2	77.7	74	66.5	54.5	42.5	41.3	36.3	38
11	86.6	68.9	59.5	73.5	72.5	66.7	75.2	75.4	74.1
29	85.5	66.1	63.5	58.0	57.2	46.6	46.4	45.9	47.8
15	88.3	69.4	61.2	65.6	55.6	69.2	63.1	80.6	70.2
17	85.6	73.1	64.7	49.6	42.1	46.4	52.6	55.2	59.8
Mean	86.9	72.9	64.6	60.0	54.3	51.6	52.7	54.6	54.5
Std.Dev.	2.0	6.1	5.0	10.5	10.9	13.1	14.2	19.7	16.0
S.E.M.	0.8	2.5	2.1	4.3	4.5	5.3	5.8	8.0	6.6

Table 74. Oxygen Saturation (percent) of Portal Venous Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	84.3	69.9	63.8	40	45.4	31.8	38	39.9	46.9
24	87.1	73.1	64.1	68.8	61.8	44.5	39.9	42.2	34.4
27	83.5	73.3	57.4	43.5	40.2	34.8	31.2	28.7	24.6
28	83.9	71.2	68.0	73.0	71.1	64.3	70.4	71.6	72.5
30	84.6	69.5	64.8	61.2	50.2	46.1	57.1	58.5	72.5
Mean	84.7	71.4	63.6	57.3	53.7	44.3	47.3	48.2	50.2
Std.Dev.	1.4	1.8	3.9	14.9	12.6	12.8	16.1	16.9	21.9
S.E.M.	0.6	0.8	1.7	6.7	5.6	5.7	7.2	7.6	9.8

None of the groups of animals displayed a significant change in SpO_2 on Day 3. The endotoxin did not bring about a fall in SpO_2 in either the Group I animals (Table 75) or the Group II animals (Table 76). All mean saturations at the measured times remained within 8 % of baseline levels in all groups.

Table 75. Oxygen Saturation (percent) of Portal Venous Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	85.1	NA	NA	72.2	73.4	75.0	71.0	NA	86.2
8	82.8	75.9	85.5	79.8	79.3	78.5	66.5	78.9	82.0
14	89.6	89.4	88.7	87.6	89.7	89.0	92.9	91.5	91.4
25	84.2	66.4	77.0	81.5	78.5	80.5	79.5	84.2	82.2
26	78.0	72.5	81.2	73.9	67.7	70.6	70.6	71.2	73.4
Mean	83.9	76.1	83.1	79.0	77.7	78.7	76.1	81.5	83.0
Std.Dev.	4.2	9.7	5.1	6.2	8.2	6.9	10.5	8.6	6.6
S.E.M.	1.9	4.4	2.3	2.8	3.6	3.1	4.7	3.8	3.0

Table 76. Oxygen Saturation (percent) of Portal Venous Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	80.3	75.9	76.9	71.3	78.6	81.8	84.5	83.1	83.5
9	86.6	79.7	83.4	84.1	86.6	83.7	82.9	81.8	84.1
11	NA	84.9	84.8	NA	NA	81.1	87.7	NA	NA
29	83.6	78.4	88.1	84.8	86.4	83.5	85.7	87	87.2
15	88.4	83.0	77.2	78.9	74.3	71.4	80.8	80.5	81.6
17	83.1	89.8	91.5	88.1	86.6	87.4	88.4	88.9	86.6
Mean	83.2	83.1	83.3	83.2	83.5	83.8	84.6	84.4	84.6
Std.Dev.	3.2	5.0	5.8	6.6	5.7	5.4	2.9	3.6	2.3
S.E.M.	1.4	2.2	2.6	2.9	2.6	2.4	1.3	1.6	1.0

Table 77. Oxygen Saturation (percent) of Portal Venous Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	91.0	88.4	89.2	88.7	89.2	90.0	85.5	88.0	87.1
24	85.8	89.6	83.5	77.6	82.2	79.5	80.5	83.0	76.9
27	78.1	75.8	74.3	80.6	81.2	80.5	81.9	81.3	79.9
28	83.2	81.2	79.7	78.4	80.6	79.2	79.0	78.9	80.5
30	82.4	81.4	84.3	82.5	85.2	83.6	84.1	83.5	82.9
Mean	84.1	83.3	82.2	81.6	83.7	82.6	82.2	82.9	81.5
Std.Dev.	4.8	5.7	5.6	4.4	3.6	4.5	2.6	3.4	3.8
S.E.M.	2.1	2.6	2.5	2.0	1.6	2.0	1.2	1.5	1.7

I. Hemoglobin Concentration

The hemoglobin concentration (Hgb) for experimental and control animals are given. During hemorrhagic shock, a substatial hemoconcentration effect took place with a rising Hgb seen in both Group II (Table 79)(not statistically significant compared to Group I) and Group III (Table 80)($p < 0.05$ compared to Group I) animals. Group II began with Hgb of 10.7±0.9 g/dl at T=4 which rose to 12.7±1.4 g/dl at T=8. Group III

similarly climbed from 11.0±0.5 g/dl to 13.1±1.7 g/dl. Control animals in Group I (Table 78) showed no rise in Hgb during four hours of anaesthesea.

Figure 15. Hemoglobin Concentration in Arterial Blood for T=4 to T=8 (Day 1) - Hemorrhage

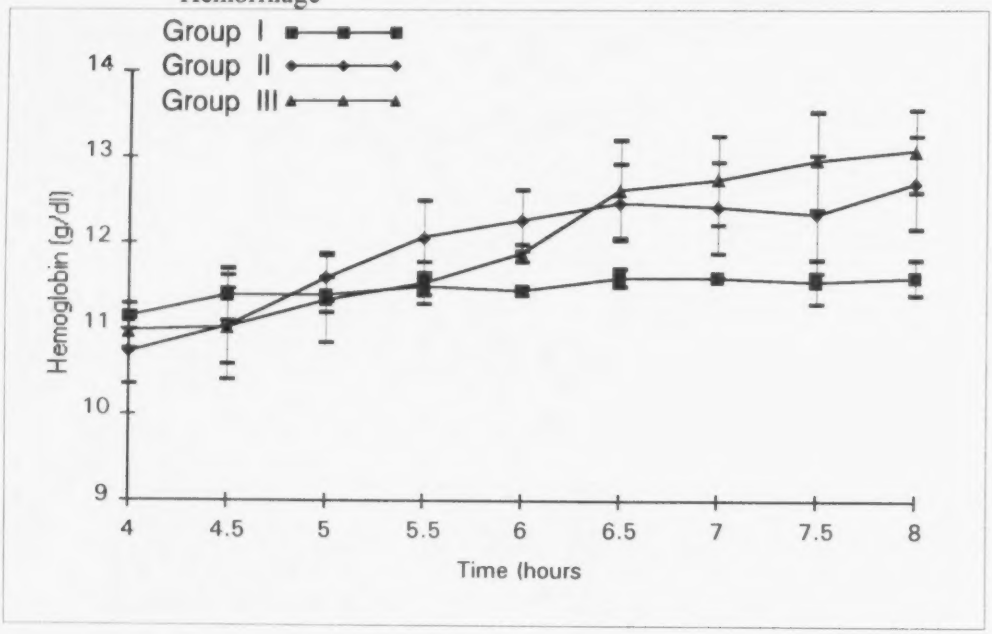


Table 78. Hemoglobin Concentration (g/dl) in Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	11	11.1	11.6	11.6	11.5	11.5	11.6	11.3	11.4
26	11.3	11.7	11.2	11.4	11.4	11.7	11.6	11.8	11.8
Mean	11.15	11.4	11.4	11.5	11.45	11.6	11.6	11.55	11.6
Std.Dev.	0.21	0.42	0.28	0.14	0.07	0.14	0.00	0.35	0.28
S.E.M.	0.15	0.30	0.20	0.10	0.05	0.10	0.00	0.25	0.20

Table 79. Hemoglobin Concentration (g/dl) in Arterial Blood of Group II for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	11.7	11.5	12.4	12.5	12.3	12.7	12.9	13.5	13.3
9	10.9	10.6	11.2	11.7	12.1	12.1	12.5	12.5	12.7
11	10.4	10.5	11.3	12	11.2	12.8	11.7	10.9	12.1
29	9.3	9.4	10.6	11.1	12.3	10.9	10.6	10.1	10.7
15	10.3	12.6	11.8	11.2	11.9	12.1	12.3	12.3	12.6
17	11.8	11.6	12.3	13.9	13.8	14.2	14.5	14.7	14.8
Mean	10.73	11.03	11.60	12.07	12.27	12.47	12.42	12.33	12.70
Std.Dev.	0.94	1.11	0.70	1.04	0.85	1.09	1.30	1.68	1.35
S.E.M.	0.39	0.45	0.28	0.42	0.35	0.44	0.53	0.68	0.55

Table 80. Hemoglobin Concentration (g/dl) in Arterial Blood of Group III for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	11.7	10.7	12	11.7	11.7	11.5	12.1	12.4	13.3
24	11	10.4	10.5	11.5	11.6	14.5	14.5	14.8	14.2
27	11.1	13.4	12.9	11.7	12.1	11.4	11.4	11.3	11.3
28	10.5	10.3	10.1	10.7	11.9	12.6	13.1	13.5	13.2
30	10.6	10.3	11.2	12.1	12.1	13.1	12.6	12.8	13.4
Mean	10.98	11.02	11.34	11.54	11.88	12.62	12.74	12.96	13.08
Std.Dev.	0.48	1.34	1.13	0.52	0.23	1.28	1.17	1.30	1.07
S.E.M.	0.21	0.60	0.51	0.23	0.10	0.57	0.52	0.58	0.48

On Day 3, it was evident that the animals previously bled (Groups II and iII) began with a lower baseline Hgb at T=48 than the animals that had not been bled (Group I). Group I (Table 81) began at 11.3±1.3 g/dl, Group II (Table 82) at 8.83±0.4 g/dl, and Group III (Table 83) at 9.76±1.2g/dl. This was likely due to damage of RBCs sustained during hemorrhage and reinfusion as well as the loss of small amounts of blood which formed clot in the blood bags. An analysis of covariance was therefore utilized to ascertain statistical significance.

While the Group III animals' Hgb did not change significantly over the four hour anaesthetic period, both groups of animals receiving endotoxin showed immediate and sustained elevations in Hgb due to a hemoconcentrating effect. Group I rose to 13.4±2.0 g/dl at T=48.5 ($p < 0.01$ compared to Group III) while Group II rose to 11.9±0.3 g/dl at T=48.5 ($p < 0.01$ compared to Group III). These differences held true at T=52. While both of these increases were significant, Group II demonstrated a greater absolute elevation in Hgb than Group I ($p < 0.05$ at T=48.5).

Figure 16. Hemoglobin Concentration in Arterial Blood for T=48 to T=52 (Day 3) - Endotoxin Infusion

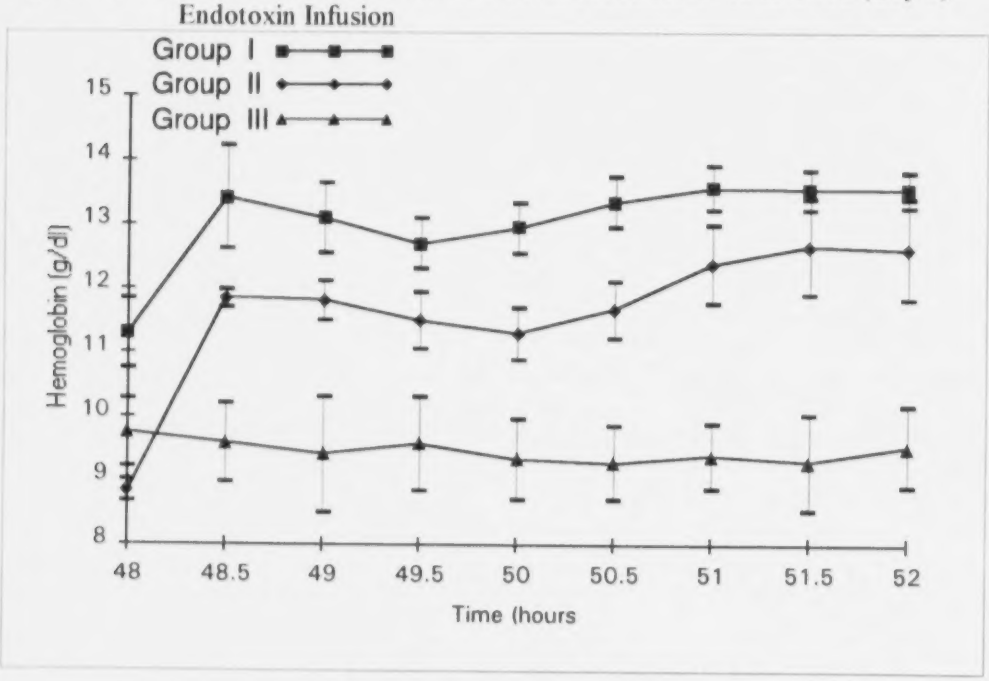


Table 81. Hemoglobin Concentration (g/dl) in Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	11.1	13.6	13.1	12.4	12.8	13.1	13.5	13.6	13.6
8	11.2	13	13.2	12.8	12.9	13.1	13.3	13.3	13.4
10	11.7	12.3	12.1	12.3	12.4	12.8	13.1	12.8	12.8
14	13.3	17.2	15.6	14.4	14.5	14.9	14.8	14.7	14.6
25	9.2	12.6	11.9	11.5	11.7	12.2	12.5	12.8	12.9
26	11.3	11.8	12.7	12.8	13.4	14	14.2	14.1	14
Mean	11.30	13.42	13.10	12.70	12.95	13.35	13.57	13.55	13.55
Std.Dev.	1.31	1.95	1.33	0.96	0.95	0.96	0.82	0.75	0.68
S.E.M.	0.54	0.80	0.54	0.39	0.39	0.39	0.33	0.31	0.28

Table 82. Hemoglobin Concentration (g/dl) in Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	8.8	12.1	11.9	11.8	12.1	11.5	12.2	12.3	12.7
9	9.1	12	12.7	12.2	12.9	13.7	14.6	16.1	16.4
11	9.5	11.9	11.4	11	10.8	11.2	13.7	13.1	12.1
29	8.4	12	11.2	10.7	10.7	12	11.9	12	11.9
15	8.5	11.2	11	10.2	10.2	10.7	11	10.9	11.2
17	8.7	11.9	12.7	13.1	11.1	11	10.9	11.6	11.4
Mean	8.83	11.85	11.82	11.50	11.30	11.68	12.38	12.67	12.62
Std.Dev.	0.41	0.33	0.75	1.07	1.01	1.08	1.49	1.83	1.93
S.E.M.	0.17	0.13	0.30	0.44	0.41	0.44	0.61	0.75	0.79

Table 83. Hemoglobin Concentration (g/dl) in Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	11.5	11.9	12.7	12.1	11.1	11	10.9	11.6	11.4
24	9.2	9.3	7.8	8	7.7	7.6	8	7	7.5
27	9.9	8.9	8.3	9.1	9.2	9.9	9.7	9.7	9.7
28	9.9	9.5	10	10.2	10.4	9.4	9.8	9.6	10.1
30	8.3	8.4	8.3	8.5	8.3	8.5	8.6	8.6	9
Mean	9.76	9.6	9.42	9.58	9.34	9.28	9.4	9.3	9.54
Std.Dev.	1.17	1.35	2.01	1.63	1.42	1.30	1.13	1.68	1.44
S.E.M.	0.52	0.60	0.90	0.73	0.63	0.58	0.50	0.75	0.64

J. Content of Oxygen in Arterial Blood

Since the PaO_2 and the SaO_2 of the animals were kept constant and similar among groups, the changes in CaO_2 mimic those of the hemoglobin concentration. During the hemorrhagic shock of Day 1, animals which were bled displayed a steady rise in arterial blood oxygen content (CaO_2) over the four hour period (Figure 17). Animals not bled (Table 84) did not show this rise. Group II animals (Table 85) went from 14.7±1.2 mgO_2/dl at T=4 to 17.3±1.9 mgO_2/dl at T=8, and Group III (Table 86) increased from 15.1 mgO_2/dl at T=4 to 18.0±1.6 mgO_2/dl at T=8. These changes, however, did not reach statistical significance.

Figure 17. Oxygen Content in Arterial Blood for T=4 to T=8 (Day 1) - Hemorrhage

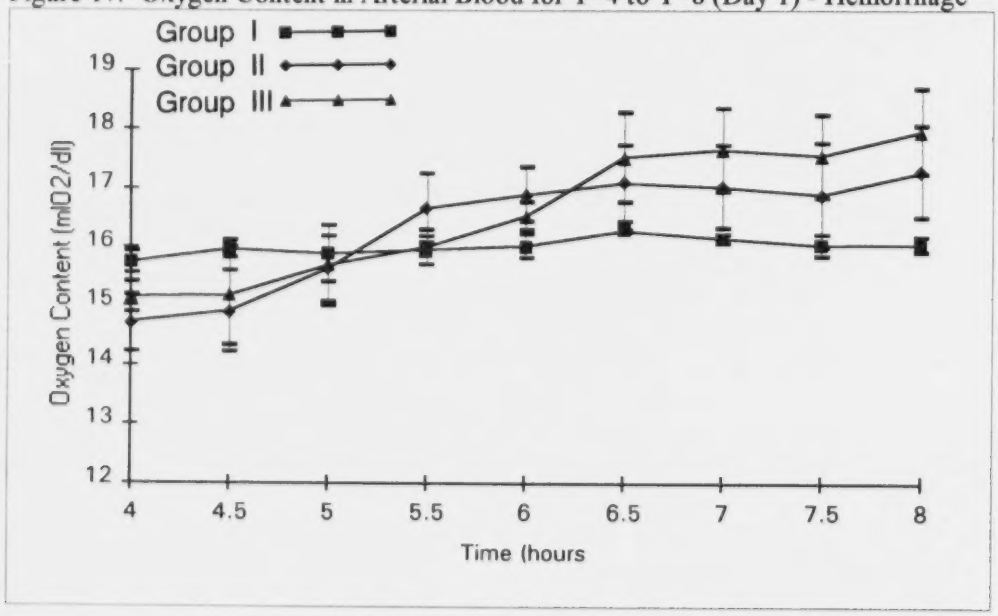


Table 84. Oxygen Content (mlO_2/dl) of Arterial Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	15.92	15.81	16.35	16.18	16.21	16.29	16.23	15.83	15.93
26	15.56	16.10	15.40	15.71	15.82	16.27	16.08	16.24	16.19
Mean	15.74	15.96	15.88	15.95	16.02	16.28	16.15	16.04	16.06
Std.Dev.	0.25	0.20	0.67	0.33	0.27	0.02	0.11	0.29	0.19
S.E.M.	0.18	0.14	0.48	0.23	0.19	0.01	0.07	0.20	0.13

Table 85. Oxygen Content (mlO_2/dl) of Arterial Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	15.73	15.46	16.63	16.86	16.58	17.11	17.46	18.21	18.01
9	15.16	14.82	15.59	16.17	16.41	16.41	16.76	16.89	17.34
11	14.38	12.97	13.44	16.68	15.89	18.01	16.63	15.19	15.61
29	12.72	13.05	14.77	15.47	17.03	14.95	14.60	13.95	14.79
15	14.41	17.25	16.29	15.45	16.36	16.54	16.79	17.09	17.76
17	15.93	15.88	17.08	19.33	19.12	19.53	19.95	20.09	20.16
Mean	14.72	14.90	15.63	16.66	16.90	17.09	17.03	16.90	17.28
Std.Dev.	1.17	1.67	1.35	1.43	1.15	1.56	1.73	2.17	1.90
S.E.M.	0.48	0.68	0.55	0.59	0.47	0.64	0.70	0.89	0.77

Table 86. Oxygen Content (mlO_2/dl) of Arterial Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	15.93	14.37	16.50	16.27	16.15	16.07	16.58	16.88	18.00
24	15.30	14.42	14.54	15.92	15.94	19.68	19.84	19.59	19.72
27	15.31	18.52	17.91	16.30	16.83	15.83	15.80	15.59	15.38
28	14.47	14.32	14.05	14.91	16.43	17.35	18.04	18.57	18.17
30	14.71	14.25	15.44	16.60	17.29	18.74	18.05	17.18	18.59
Mean	15.14	15.18	15.69	16.00	16.53	17.53	17.66	17.56	17.97
Std.Dev.	0.57	1.87	1.55	0.66	0.54	1.67	1.55	1.55	1.60
S.E.M.	0.26	0.84	0.69	0.29	0.24	0.75	0.69	0.69	0.71

During the endotoxin infusion, the C_aO_2 of the Group I (Table 87) and Group II (Table 88) animals showed a sudden, sustained increase similar to the rise seen in Hgb. The increase in Group I from 15.6±1.7 mlO_2/dl to 18.8±2.7 mlO_2/dl at T=48.5 was significant compared with Group III ($p < 0.01$) and Group II ($p < 0.05$). The initial rise in C_aO_2 in Group II was also significant compared to Group III ($p < 0.01$). Animals in Group III (Table 89), not receiving endtoxin, maintained a steady CaO_2 of 13.7 mgO_2/dl at T=48 which varied only 0.7 mgO_2/dl over the four hours. The statistically significant difference between Group III and the other groups was maintained at T=52 ($p < 0.01$).

Figure 18. Content of Oxygen in Arterial Blood for T=48 to T=52 (Day 3) - Endotoxin Infusion

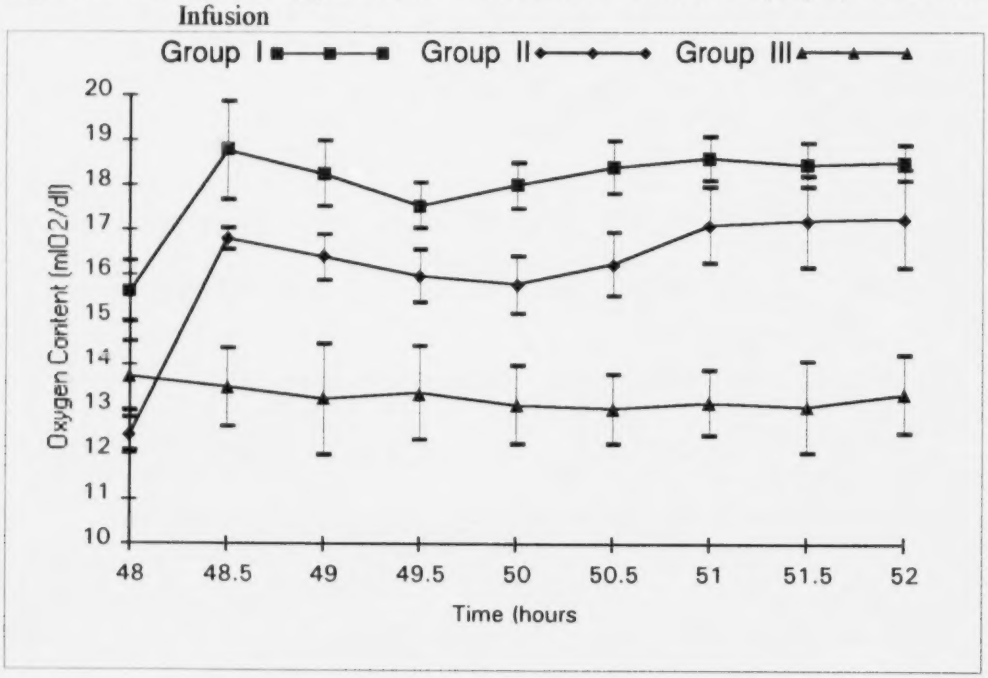


Table 87. Oxygen Content (mlO_2/dl) Arterial Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	15.35	18.77	18.12	17.23	17.64	17.91	18.24	18.48	18.57
8	15.98	18.74	18.89	17.97	17.90	17.80	18.20	17.79	18.22
10	15.69	17.22	17.12	17.15	17.61	17.63	17.75	17.20	17.32
14	18.27	24.00	21.34	19.67	20.09	20.87	20.65	20.31	20.06
25	12.90	17.26	16.18	15.87	16.31	16.85	17.31	17.71	17.87
26	15.61	16.62	17.83	17.36	18.53	19.33	19.45	19.22	19.06
Mean	15.63	18.77	18.25	17.54	18.01	18.40	18.60	18.45	18.52
Std.Dev.	1.71	2.71	1.77	1.25	1.25	1.45	1.23	1.15	0.96
S.E.M.	0.70	1.11	0.72	0.51	0.51	0.59	0.50	0.47	0.39

Table 88. Oxygen Content (mlO_2/dl) of Arterial Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	12.03	16.84	15.53	15.55	16.48	15.88	16.85	16.69	17.41
9	13.40	17.46	18.38	17.60	18.54	19.54	20.75	22.17	22.58
11	13.77	16.89	16.36	15.68	15.19	15.40	18.08	16.61	15.77
29	11.80	16.94	15.33	14.80	14.81	16.45	16.42	16.55	16.48
15	11.84	15.68	15.25	14.33	14.24	14.66	15.36	15.33	15.76
17	11.75	16.97	17.49	17.90	15.49	15.49	15.16	15.89	15.55
Mean	12.43	16.80	16.39	15.98	15.79	16.24	17.10	17.21	17.26
Std.Dev.	0.90	0.59	1.29	1.46	1.54	1.72	2.08	2.49	2.69
S.E.M.	0.37	0.24	0.53	0.60	0.63	0.70	0.85	1.02	1.10

Table 89. Oxygen Content (mlO_2/dl) of Arterial Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	16.39	16.86	17.79	16.92	15.50	15.36	15.28	16.28	15.92
24	12.88	13.09	11.09	11.11	10.81	10.67	11.11	9.97	10.57
27	13.84	12.41	11.67	12.74	12.90	13.86	13.53	13.59	13.50
28	13.88	13.33	13.99	14.19	14.56	13.13	13.68	13.41	14.05
30	11.63	11.77	11.60	11.89	11.67	12.03	12.11	12.03	12.63
Mean	13.73	13.49	13.23	13.37	13.09	13.01	13.14	13.05	13.33
Std.Dev.	1.75	1.98	2.79	2.29	1.95	1.78	1.60	2.31	1.96
S.E.M.	0.78	0.89	1.25	1.02	0.87	0.80	0.71	1.03	0.88

K. Delivery of Oxygen to Gut

The amount of oxygen being delivered to the gastrointestinal tract (DO_2) by way of the craniomesenteric artery is shown for Day 3 in Table 90. Because the calculation for this value incorporates the craniomesenteric artery flow rate, which is best standardized as a percent of baseline, values for DO_2 are recalculated as percent of baseline in Tables 91, 92, and 93. An initial decline in DO_2 was noted in both groups receiving endotoxin. Group I fell to 79.4±12% of baseline at T=48.5 and Group II fell to 74.0±13% (both $p < 0.05$ compared to Group III). After this, however, Group I recovered to a level above baseline of 102.2±8% while Group II remained at a reduced DO_2 of 69.47±25.4 ($p < 0.01$) which persisted for the duration of the monitored period ($p < 0.01$ at T=52).

Figure 19. Gut Oxygen Delivery for T=48 to T=52 (Day 3) - Endotoxin Infusion

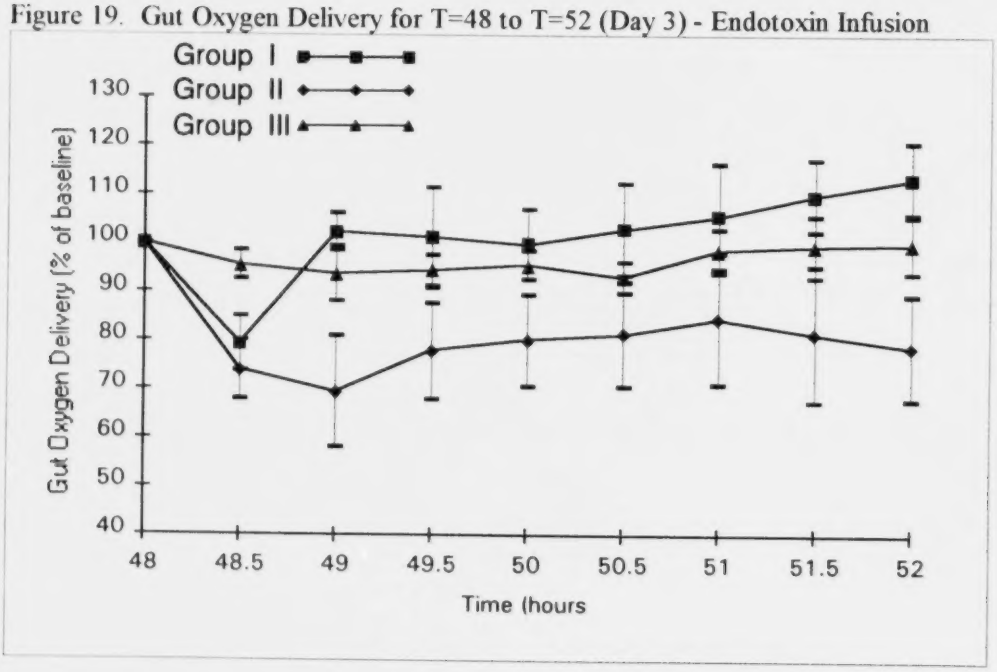


Table 90. Gut Oxygen Delivery (mlO2/min) for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
Group I									
7	112.7	98.6	103.5	82.5	91.4	91.9	88.8	105.3	122.6
8	45.2	27.4	46.3	42.8	47.2	47.9	46.2	51.6	51.9
10	112.1	82.7	124.7	100.3	106.4	92.9	92.0	100.1	95.4
14	129.7	122.7	123.1	126.9	115.5	140.6	172.2	155.8	150.2
25	80.1	58.7	80.2	87.8	81.0	79.7	82.6	87.2	93.6
26	81.4	70.5	91.8	115.9	103.8	113.1	109.3	108.4	112.1
Group II									
5	91.4	73.1	105.6	96.4	97.2	104.8	124.7	121.8	114.9
9	92.5	62.5	72.0	54.9	69.5	62.3	54.8	46.3	55.3
11	143.1	138.0	85.6	109.8	105.3	117.2	115.2	98.0	100.0
29	184.1	128.6	122.0	121.4	132.0	115.8	112.6	111.2	113.7
15	106.5	60.5	57.1	59.6	54.1	58.8	70.7	77.3	76.0
17	71.7	52.4	31.3	74.8	74.2	75.9	74.4	74.4	60.0
Group III									
20	140.0	139.1	149.3	140.7	131.3	129.2	125.1	137.7	132.2
24	77.2	72.2	64.8	64.7	71.6	66.5	72.6	61.8	66.0
27	130.8	111.2	100.2	117.2	113.2	116.3	127.1	135.9	126.3
28	76.4	76.0	78.4	75.2	78.6	72.2	73.9	73.7	77.3
30	95.4	95.3	94.0	95.1	96.9	98.6	110.2	113.1	116.2

Table 91. Gut Oxygen Delivery (percent of baseline) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51.0	51.5	52.0
7	100	87.5	91.8	73.3	81.1	81.5	78.8	93.5	108.8
8	100	60.5	102.3	94.6	104.5	105.9	102.2	114.1	114.8
10	100	73.8	111.3	89.5	94.9	82.9	82.1	89.3	85.2
14	100	94.6	95.0	97.8	89.1	108.4	132.8	120.1	115.8
25	100	73.2	100.1	109.6	101.2	99.5	103.0	108.8	116.9
26	100	86.6	112.8	142.5	127.6	139.0	134.4	133.3	137.8
Mean	100	79.4	102.2	101.2	99.7	102.9	105.6	109.8	113.2
Std.Dev.	0	12.5	8.5	23.5	16.0	21.0	23.9	16.5	16.9
S.E.M.	0	5.6	3.8	10.5	7.2	9.4	10.7	7.4	7.6

Table 92. Gut Oxygen Delivery (percent of baseline) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48.0	48.5	49.0	49.5	50.0	50.5	51.0	51.5	52.0
5	100	80.0	115.5	105.4	106.4	114.7	136.4	133.3	125.7
9	100	67.6	77.9	59.4	75.2	67.4	59.2	50.1	59.8
11	100	96.5	59.8	76.7	73.6	81.9	80.5	68.5	69.9
29	100	69.8	66.3	65.9	71.7	62.9	61.2	60.4	61.8
15	100	56.9	53.6	56.0	50.8	55.2	66.4	72.6	71.4
17	100	73.1	43.7	104.4	103.5	105.9	103.8	103.7	83.7
Mean	100	74.0	69.5	78.0	80.2	81.3	84.6	81.4	78.7
Std.Dev.	0	13.4	25.4	22.0	21.1	24.2	30.3	31.2	24.5
S.E.M.	0	6.0	11.3	9.9	9.5	10.8	13.6	13.9	11.0

Table 93. Gut Oxygen Delivery (percent of baseline) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48.0	48.5	49.0	49.5	50.0	50.5	51.0	51.5	52.0
20	100	99.4	106.6	100.5	93.8	92.3	89.4	98.4	94.4
24	100	93.6	84.0	83.9	92.8	86.1	94.0	80.1	85.5
27	100	85.0	76.6	89.6	86.6	88.9	97.2	103.9	96.6
28	100	99.5	102.6	98.5	103.0	94.6	96.7	96.6	101.2
30	100	99.9	98.5	99.7	101.5	103.4	115.5	118.5	121.8
Mean	100	95.5	93.7	94.4	95.5	93.1	98.6	99.5	99.9
Std.Dev.	0	6.4	12.8	7.3	6.8	6.6	10.0	13.8	13.5
S.E.M.	0	2.9	5.7	3.3	3.0	3.0	4.5	6.2	6.0

L. Content of Oxygen in Portal Venous Blood

Those animals placed into hemorrhagic shock on Day 1 experienced a dramatic decrease in their portal venous oxygen content (CpO_2) as shown in Figure 20. Both Group II (Table 95) and Group III (Table 96) animals experienced their minimum CpO_2 at T=6.5 . Group II animals fell from 12.7±1.1 to 8.7±2.3 mlO_2/dl ($p < 0.05$ compared to Group I) while Group III went from 12.6±0.6 to 7.65±2.5 mlO_2/dl ($p < 0.05$ compared to

Group I). Group I animals (Table 94) remained steady from 14.1±.1 mlO_2/dl and varied only 0.2 mlO_2/dl.

Figure 20. Oxygen Content of Portal Venous Blood for T=4 to T=8 (Day 1) - Hemorrhage

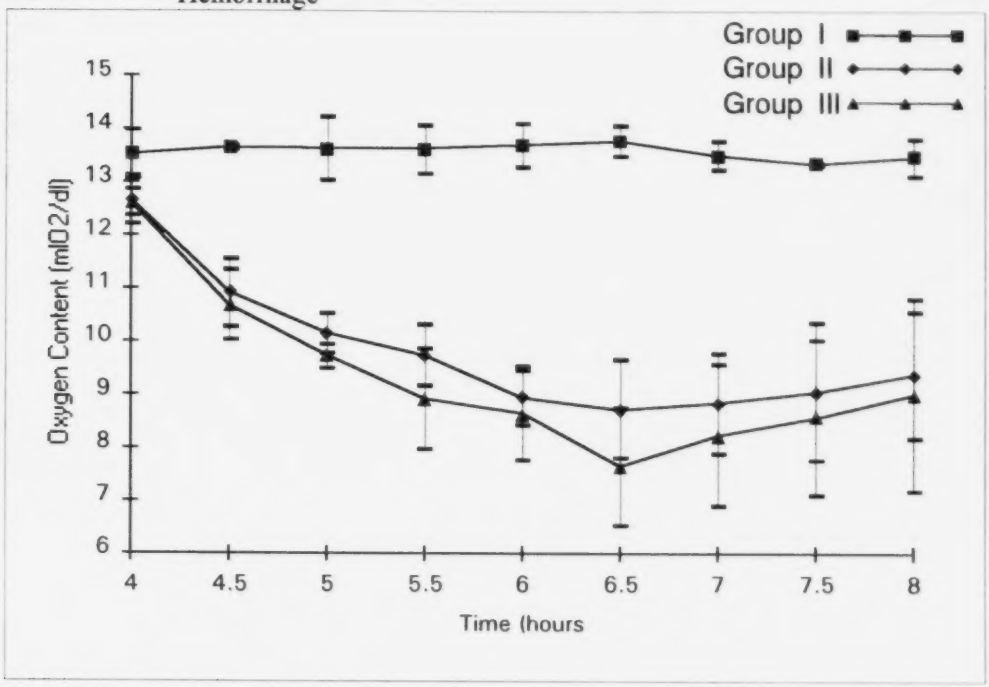


Table 94. Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	13.96	13.60	14.21	14.08	14.12	14.07	13.77	13.37	13.82
26	13.08	13.70	13.05	13.17	13.27	13.48	13.23	13.31	13.12
Mean	13.52	13.65	13.63	13.63	13.70	13.78	13.50	13.34	13.47
Std.Dev.	0.63	0.07	0.82	0.64	0.60	0.42	0.38	0.04	0.50
S.E.M.	0.44	0.05	0.58	0.45	0.42	0.30	0.27	0.03	0.35

Table 95. Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	13.53	12.83	10.88	7.90	7.34	6.58	6.62	6.27	6.67
9	13.35	11.17	11.23	10.54	8.93	6.98	7.00	6.16	6.54
11	12.23	9.80	9.10	11.94	11.00	11.56	11.92	11.15	12.14
29	10.82	8.44	9.13	8.73	9.53	6.90	6.69	6.31	6.96
15	12.35	11.83	9.78	9.95	8.96	11.33	10.50	13.44	11.98
17	13.69	11.48	10.77	9.33	7.87	8.92	10.32	10.98	11.96
Mean	12.66	10.92	10.15	9.73	8.94	8.71	8.84	9.05	9.38
Std.Dev.	1.09	1.56	0.93	1.42	1.29	2.27	2.34	3.19	2.91
S.E.M.	0.45	0.64	0.38	0.58	0.53	0.93	0.96	1.30	1.19

Table 96. Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	13.37	10.14	10.38	6.36	7.23	4.99	6.27	6.74	8.48
24	13.00	10.31	9.12	10.72	9.71	8.73	7.83	8.45	6.61
27	12.57	13.28	10.02	6.90	6.60	5.39	4.84	4.42	3.80
28	11.95	9.94	9.31	10.59	11.46	10.97	12.48	13.08	12.95
30	12.17	9.71	9.83	10.03	8.24	8.19	9.75	10.15	13.16
Mean	12.61	10.68	9.73	8.92	8.65	7.65	8.23	8.57	9.00
Std.dev.	0.58	1.47	0.51	2.11	1.96	2.48	3.00	3.29	4.06
S.E.M.	0.26	0.66	0.23	0.95	0.88	1.11	1.34	1.47	1.82

During T=48 to T=52, endotoxin was seen to bring about an increase in CpO_2 (Figure 21). While Group III animals showed only a small decrease in CpO_2 (Table 99) over the four hours of anaesthesia, Group I animals (Table 97) demonstrated an increase from 12.8±2.1 mlO_2/dl at T=48 to 15.41 mlO_2/dl at T=52, and Group II (Table 98) animals increased from 10.0±0.5 to 14.6±2.4 mlO_2/dl. Both of these increases were statistically significant as compared to Group III ($p < 0.05$ at T=48.5, and $p < 0.01$ at T=52). Group II animals demonstrated a greater absolute elevation of CpO_2 than their Group I counterparts but this did not reach statistical significance.

Figure 21. Oxygen Content of Portal Venous Blood for T=48 to T=52 (Day 3) - Endotoxin Infusion

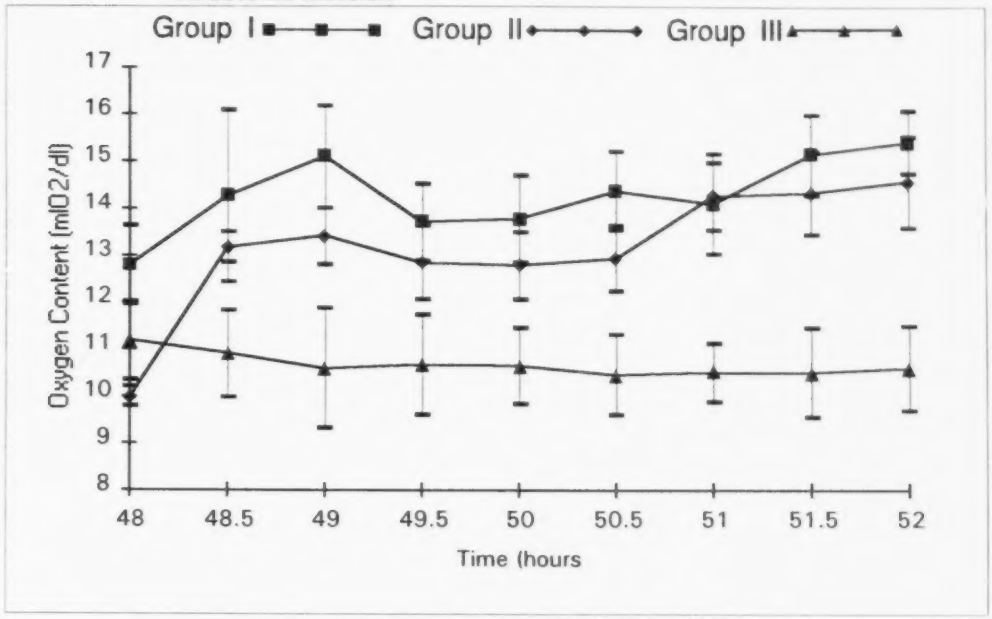


Table 97. Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	12.81	NA	NA	12.11	12.73	13.30	12.96	NA	15.87
8	12.58	13.36	15.29	13.84	13.85	13.92	11.96	14.20	14.87
14	16.14	20.77	18.71	17.06	17.60	17.95	18.61	18.21	18.06
25	10.53	11.33	12.42	12.70	12.44	13.31	13.46	14.60	14.36
26	11.94	11.59	13.96	12.81	12.27	13.37	13.56	13.58	13.90
Mean	12.80	14.26	15.10	13.71	13.78	14.37	14.11	15.15	15.41
Std.Dev.	2.07	4.43	2.68	1.98	2.22	2.02	2.59	2.09	1.65
S.E.M.	0.84	1.81	1.09	0.81	0.91	0.82	1.06	0.85	0.67

Table 98. Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	9.61	12.45	12.41	11.40	12.90	12.78	13.99	13.86	14.38
9	10.71	12.95	14.34	13.90	15.13	15.51	16.36	17.79	18.63
11	NA	13.69	13.11	NA	NA	12.32	16.25	NA	NA
29	9.55	12.75	13.39	12.31	12.55	13.58	13.82	14.15	14.06
15	10.24	12.62	11.52	10.94	10.30	10.37	12.08	11.93	12.41
17	9.82	14.49	15.76	15.63	13.05	13.05	13.08	13.98	13.38
Mean	9.99	13.16	13.42	12.84	12.78	12.93	14.26	14.34	14.57
Std.Dev.	0.49	0.78	1.49	1.93	1.72	1.68	1.72	2.13	2.39
S.E.M.	0.20	0.32	0.61	0.79	0.70	0.68	0.70	0.87	0.98

Table 99. Oxygen Content (mlO_2/dl) of Portal Venous Blood of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	14.22	14.28	15.36	14.56	13.45	13.45	12.65	13.85	13.47
24	10.73	11.33	8.87	8.44	8.62	8.22	8.76	7.92	7.85
27	10.49	9.17	8.38	9.96	10.15	10.81	10.78	10.70	10.51
28	11.19	10.48	10.82	10.85	11.37	10.11	10.51	10.28	11.03
30	9.30	9.30	9.52	9.54	9.64	9.69	9.85	9.77	10.14
Mean	11.19	10.91	10.59	10.67	10.65	10.46	10.51	10.51	10.60
Std.Dev.	1.84	2.08	2.82	2.34	1.85	1.92	1.43	2.15	2.01
S.E.M.	0.82	0.93	1.26	1.05	0.83	0.86	0.64	0.96	0.90

M. Gradient of Oxygen Content of Arterial vs. Portal Venous Blood

Hemorrhagic shock caused the gradient of the content of oxygen in arterial versus portal venous blood ($C_{a\text{-}p}O_2$) to rise (Figure 22). The Group I animals (Table 100) had a very small variation of $C_{a\text{-}p}O_2$, beginning at 2.22±0.4 mlO_2/dl and ending with 2.59±0.7 mlO_2/dl at T=8. Group II animals (Table 101) began at a level of 20.6±0.17 mlO_2/dl at T=4, and ended at 7.90±2.6 mlO_2/dl ($p < 0.05$ compared to Group I). Group III animals

(Table 102) rose from 2.53±0.16 mlO_2/dl at T=4, to 8.97±3.6 mlO_2/dl at T=8 ($p < 0.05$ compared to Group I). Both groups showed a maximum gradient at T=6.5 - Group II at 8.38±2.2 mlO_2/dl and Group III at 9.88±1.97 mlO_2/dl.

Figure 22. Arterial-Portal Oxygen Content Gradient for T=4 to T=8 (Day 1) - Hemorrhage

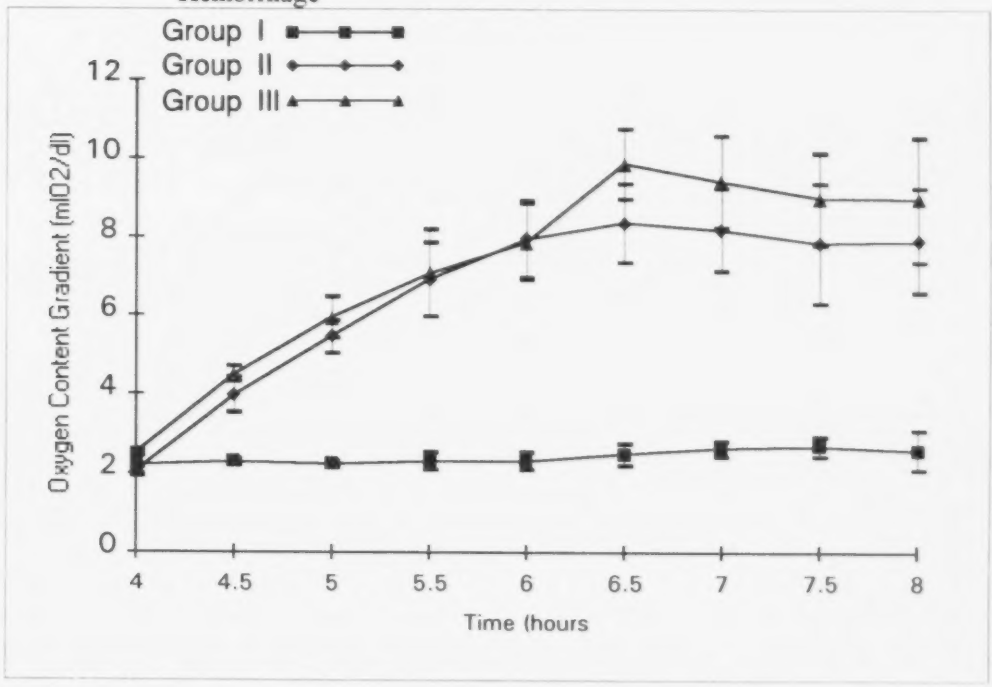


Table 100. Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	1.95	2.21	2.15	2.10	2.09	2.22	2.46	2.46	2.11
26	2.48	2.40	2.35	2.54	2.55	2.79	2.85	2.93	3.07
Mean	2.22	2.30	2.25	2.32	2.32	2.50	2.65	2.69	2.59
Std.Dev.	0.37	0.13	0.14	0.31	0.33	0.40	0.28	0.33	0.68
S.E.M.	0.26	0.09	0.10	0.22	0.23	0.28	0.19	0.23	0.48

Table 101. Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	2.20	2.64	5.75	8.97	9.24	10.53	10.84	11.94	11.34
9	1.81	3.65	4.36	5.63	7.47	9.43	9.76	10.73	10.79
11	2.15	3.17	4.33	4.74	4.88	6.46	4.71	4.04	3.47
29	1.91	4.61	5.63	6.74	7.49	8.05	7.91	7.65	7.84
15	2.05	5.42	6.51	5.50	7.39	5.21	6.29	3.65	5.78
17	2.24	4.40	6.31	10.00	11.26	10.61	9.63	9.12	8.19
Mean	2.06	3.98	5.48	6.93	7.96	8.38	8.19	7.85	7.90
Std.Dev.	0.17	1.02	0.94	2.10	2.13	2.22	2.34	3.43	2.98
S.E.M.	0.08	0.46	0.42	0.94	0.95	0.99	1.05	1.53	1.33

Table 102. Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	2.56	4.23	6.12	9.91	8.92	11.08	10.31	10.14	9.52
24	2.30	4.12	5.42	5.20	6.23	10.95	12.00	11.14	13.10
27	2.74	5.24	7.89	9.39	10.23	10.44	10.96	11.17	11.58
28	2.52	4.37	4.74	4.31	4.97	6.38	5.56	5.49	5.22
30	2.53	4.54	5.61	6.57	9.06	10.55	8.30	7.03	5.43
Mean	2.53	4.50	5.96	7.08	7.88	9.88	9.43	9.00	8.97
Std.Dev.	0.16	0.44	1.19	2.49	2.19	1.97	2.55	2.59	3.57
S.E.M.	0.07	0.20	0.53	1.11	0.98	0.88	1.14	1.16	1.59

The $C_{a\text{-}p}O_2$ gradient increased in animals that received endotoxin on Day 3 (Figure 23). This measurement remained relatively constant in Group III (Table 105) animals with an initial level of 2.54±0.5 mlO_2/dl and variation of 0.2 mlO_2/dl over the four hours. Group I animals (Table 103) began at 2.82±0.7, rose to 4.90±1.2 at T=48.5 ($p < 0.05$ compared to Group II and $p < 0.01$ compared to Group III)., and ended at T=52 with 3.34±1.2 mlO_2/dl. Group II (Table 104) started at 2.18±0.4, rose to 3.64±0.8, and finished at 2.98±0.7 mlO_2/dl at T=52. Throughout the four hours, Group I maintained a

greater mean value than Group II which was statistically significant ($p < 0.05$) at T=48.5 and at T=51.

Figure 23. Arterial-Portal Oxygen Content Gradient for T=48 to T=52 (Day 3) - Endotoxin Infusion

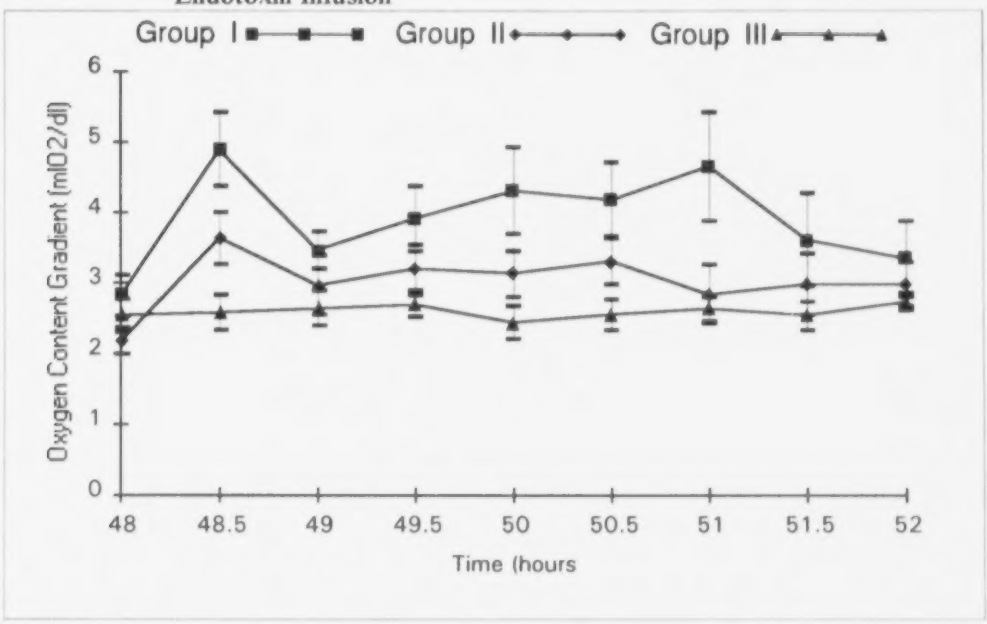


Table 103. Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	2.54	NA	NA	5.12	4.91	4.61	5.28	NA	2.70
8	3.40	5.39	3.60	4.13	4.05	3.89	6.24	3.58	3.35
14	2.13	3.23	2.64	2.61	2.49	2.91	2.04	2.09	2.00
25	2.37	5.93	3.76	3.17	3.86	3.54	3.85	3.11	3.51
26	3.67	5.03	3.86	4.55	6.26	5.96	5.90	5.65	5.16
Mean	2.82	4.90	3.46	3.92	4.31	4.18	4.66	3.61	3.34
Std.Dev.	0.68	1.17	0.56	1.02	1.39	1.17	1.73	1.49	1.18
S.E.M.	0.30	0.52	0.25	0.46	0.62	0.52	0.77	0.67	0.53

Table 104. Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	2.41	4.39	3.13	4.14	3.59	3.11	2.85	2.83	3.04
9	2.69	4.51	4.04	3.70	3.42	4.03	4.39	4.38	3.95
11	NA	3.20	3.25	NA	NA	3.09	1.83	NA	NA
29	2.25	4.19	1.93	2.49	2.27	2.87	2.60	2.40	2.42
15	1.60	3.06	3.73	3.39	3.94	4.29	3.29	3.41	3.35
17	1.93	2.48	1.74	2.28	2.45	2.44	2.08	1.91	2.17
Mean	2.18	3.64	2.97	3.20	3.13	3.30	2.84	2.99	2.98
Std.Dev.	0.42	0.84	0.94	0.80	0.74	0.71	0.93	0.95	0.71
S.E.M.	0.19	0.37	0.42	0.36	0.33	0.32	0.41	0.43	0.32

Table 105. Arterial - Portal Oxygen Content Gradient (mlO_2/dl) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	2.17	2.58	2.43	2.36	2.05	1.91	2.63	2.42	2.45
24	2.15	1.76	2.22	2.66	2.20	2.44	2.35	2.05	2.72
27	3.35	3.25	3.29	2.78	2.75	3.05	2.75	2.89	2.98
28	2.70	2.85	3.17	3.34	3.19	3.02	3.17	3.13	3.01
30	2.34	2.47	2.08	2.35	2.03	2.33	2.26	2.26	2.49
Mean	2.54	2.58	2.64	2.70	2.44	2.55	2.63	2.55	2.73
Std.Dev.	0.50	0.55	0.56	0.41	0.51	0.50	0.36	0.45	0.26
S.E.M.	0.23	0.25	0.25	0.18	0.23	0.22	0.16	0.20	0.12

N. Oxygen Uptake of Gut

Rate of uptake of oxygen of the gut (VO_{2g}) was calculated as the product of the arterial-portal oxygen content difference and the craniomesenteric artery flow rate. Results for Groups I, II, and III are shown in Table 106. As the CAF has been expressed as a percent of baseline in order to compensate for weight and anatomic differences in animals, the VO_{2g} is also expressed as a percent of baseline in Tables 107, 108, and 109.

Results are depicted graphically in Figure 24. Group I animals experienced an increase of VO_{2g} which peaked at 142±26 % at T=51 and finished at 116±27 %. Group II animals showed a decline in VO_{2g} which finished at 78.4±31 % at T=52. Group III animals had a steady VO_{2g} with little variation over time while under anaesthetic. Differences between Group I and Group II are statistically significant at several points ($p < 0.01$ at T=51 and $p < 0.05$ at T=52).

Because of inconsistent coupling of the flow probe on Day 1 (T=4 to T=8), the $V0_{2g}$ is not available for this time period.

Figure 24. Gut Oxygen Uptake for T=48 to T=52 (Day 3) - Endotoxin Infusion

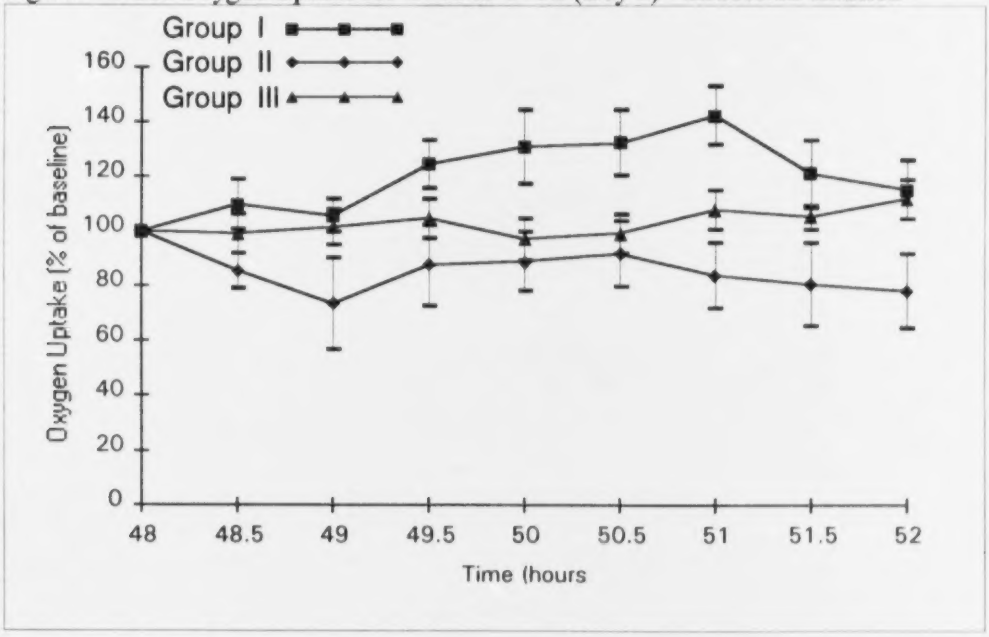


Table 106. Gut Oxygen Uptake (mlO2/min) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
Group I									
7	18.63	NA	NA	24.52	25.43	23.65	25.70	NA	17.82
8	9.62	7.86	8.81	9.84	10.69	10.45	15.85	10.39	9.54
14	15.10	16.52	15.20	16.81	14.30	19.64	16.98	16.06	14.95
25	14.73	20.16	18.64	17.52	19.20	16.73	18.34	15.32	18.39
26	19.12	21.34	19.89	30.40	35.04	34.87	33.13	31.85	30.36
Group II									
5	18.35	19.06	21.27	25.69	21.16	20.50	21.11	20.63	20.05
9	18.55	16.14	15.84	11.54	12.81	12.85	11.59	9.16	9.67
11	NA	26.15	16.99	NA	NA	23.50	11.63	NA	NA
29	35.09	31.82	15.38	20.43	20.18	20.23	17.82	16.14	16.66
15	14.40	11.81	13.95	14.10	14.98	17.21	15.11	17.18	16.12
17	11.76	7.66	3.11	9.51	11.72	11.94	10.19	8.96	8.39
Group III									
20	18.52	21.32	20.40	19.62	17.40	16.03	21.55	20.50	20.35
24	12.90	9.69	12.99	15.52	14.53	15.22	15.36	12.69	16.99
27	31.65	29.10	28.23	25.51	24.16	25.59	25.80	28.88	27.92
28	14.84	16.27	17.77	17.70	17.21	16.62	17.14	17.19	16.58
30	19.16	20.00	16.82	18.78	16.83	19.14	20.58	21.22	22.91

Table 107. Gut Oxygen Uptake (percent of baseline) of Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	100	NA	NA	131.6	136.5	126.9	138.0	NA	95.7
8	100	81.7	91.6	102.2	111.1	108.6	164.7	108.0	99.1
14	100	109.4	100.7	111.3	94.7	130.1	112.5	106.4	99.0
25	100	136.8	126.5	118.9	130.3	113.6	124.5	104.0	124.8
26	100	111.6	104.0	159.0	183.2	182.4	173.3	166.5	158.7
Mean	100	109.9	105.7	124.6	131.2	132.3	142.6	121.2	115.5
Std.Dev.	0	22.5	14.8	22.0	33.4	29.4	25.9	30.3	26.9
S.E.M.	0	9.2	6.1	9.0	13.7	12.0	10.6	12.4	11.0

Table 108. Gut Oxygen Uptake (percent of baseline) of Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	100	103.9	116.0	140.0	115.3	111.7	115.0	112.5	109.3
9	100	87.0	85.4	62.2	69.1	69.3	62.5	49.4	52.1
13	100	90.7	43.8	58.2	57.5	57.6	50.8	46.0	47.5
15	100	82.0	96.8	97.9	104.0	119.5	104.9	119.2	111.9
17	100	65.1	26.4	80.9	99.7	101.6	86.6	76.2	71.3
Mean	100	85.7	73.7	87.8	89.1	91.9	84.0	80.7	78.4
Std.Dev.	0	14.1	37.4	33.2	24.6	27.1	27.3	34.3	30.7
S.E.M.	0	6.3	16.7	14.8	11.0	12.1	12.2	15.3	13.7

Table 109. Gut Oxygen Uptake (percent of baseline) of Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	100	115.1	110.2	105.9	94.0	86.6	116.4	110.7	109.9
24	100	75.1	100.7	120.3	112.6	118.0	119.0	98.4	131.7
27	100	91.9	89.2	80.6	76.3	80.9	81.5	91.3	88.2
28	100	109.6	119.7	119.3	116.0	112.0	115.5	115.8	111.7
30	100	104.4	87.8	98.0	87.9	99.9	107.4	110.8	119.6
Mean	100	99.2	101.5	104.8	97.4	99.5	108.0	105.4	112.2
Std.Dev.	0	16.0	13.7	16.5	16.8	15.9	15.4	10.2	15.9
S.E.M.	0	7.2	6.1	7.4	7.5	7.1	6.9	4.6	7.1

O. Oxygen Extraction Ratio of Gut

During hemorrhagic shock on Day 1, an increase in the oxygen extraction ratio (O_2ER) was seen in animals that were bled (Figure 25). Group I animals (Table 110) showed very little deviation from their initial ratio of 0.107±0.02 whereas Group II animals (Table 111) went from 0.14±0.01 at T=4 to 0.456±0.17 at T=8 ($p < 0.01$ compared to Group I), and Group III (Table 112) increased from 0.147±0.01 to 0.505±0.21 ($p < 0.02$ compared to Group I).

Figure 25. Gut Oxygen Extraction Ratio for T=4 to T=8 (Day 3) - Hemorrhage

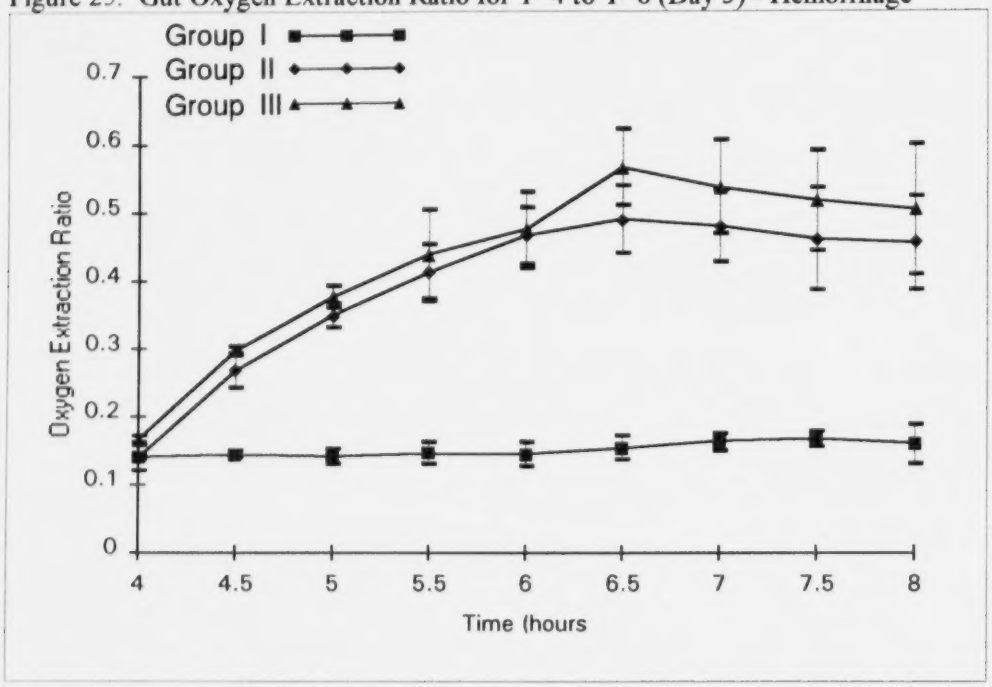


Table 110. Gut Oxygen Extraction Ratio in Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	0.123	0.140	0.131	0.130	0.129	0.136	0.151	0.156	0.132
26	0.159	0.149	0.153	0.162	0.161	0.171	0.177	0.180	0.190
Average	0.141	0.144	0.142	0.146	0.145	0.154	0.164	0.168	0.161
Std.Dev.	0.026	0.006	0.015	0.023	0.023	0.025	0.018	0.017	0.041
S.E.M.	0.018	0.004	0.011	0.016	0.016	0.018	0.013	0.012	0.029

Table 111. Gut Oxygen Extraction Ratio in Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4.0	5	5	5.5	6	6.5	7	7.5	8
5	0.140	0.170	0.346	0.532	0.557	0.615	0.621	0.656	0.630
9	0.119	0.247	0.279	0.348	0.456	0.575	0.582	0.635	0.622
11	0.150	0.244	0.323	0.284	0.307	0.358	0.283	0.266	0.222
29	0.150	0.353	0.382	0.435	0.440	0.538	0.542	0.548	0.530
15	0.142	0.314	0.400	0.356	0.452	0.315	0.375	0.213	0.325
17	0.141	0.277	0.369	0.517	0.589	0.543	0.483	0.454	0.406
Mean	0.140	0.268	0.350	0.412	0.467	0.491	0.481	0.462	0.456
Std.Dev.	0.011	0.063	0.044	0.100	0.099	0.123	0.130	0.187	0.166
S.E.M.	0.005	0.026	0.018	0.041	0.041	0.050	0.053	0.076	0.068

Table 112. Gut Oxygen Extraction Ratio in Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	0.160	0.294	0.371	0.609	0.552	0.689	0.622	0.601	0.529
24	0.150	0.286	0.373	0.327	0.391	0.557	0.605	0.569	0.665
27	0.179	0.283	0.441	0.576	0.608	0.659	0.694	0.717	0.753
28	0.174	0.306	0.337	0.289	0.303	0.368	0.308	0.296	0.287
30	0.172	0.319	0.363	0.396	0.524	0.563	0.460	0.409	0.292
Mean	0.167	0.297	0.377	0.439	0.475	0.567	0.538	0.518	0.505
Std.Dev.	0.012	0.015	0.038	0.145	0.125	0.126	0.154	0.166	0.212
S.E.M.	0.005	0.007	0.017	0.065	0.056	0.056	0.069	0.074	0.095

During endotoxic shock, changes in O_2ER were less definite than during hemorrhage (Figure 26). Group I animals (Table 113) generally showed a greater increase in O_2ER than Group II (Table 114), especially over the first 30 minutes of the experimental run. Differences were not statistically significant. Animals from Group III (Table 115), not receiving endotoxin, showed little variation over the four hours.

Figure 26. Gut Oxygen Extraction Ratio for T=48 to T=52 (Day 3) - Endotoxin Infusion

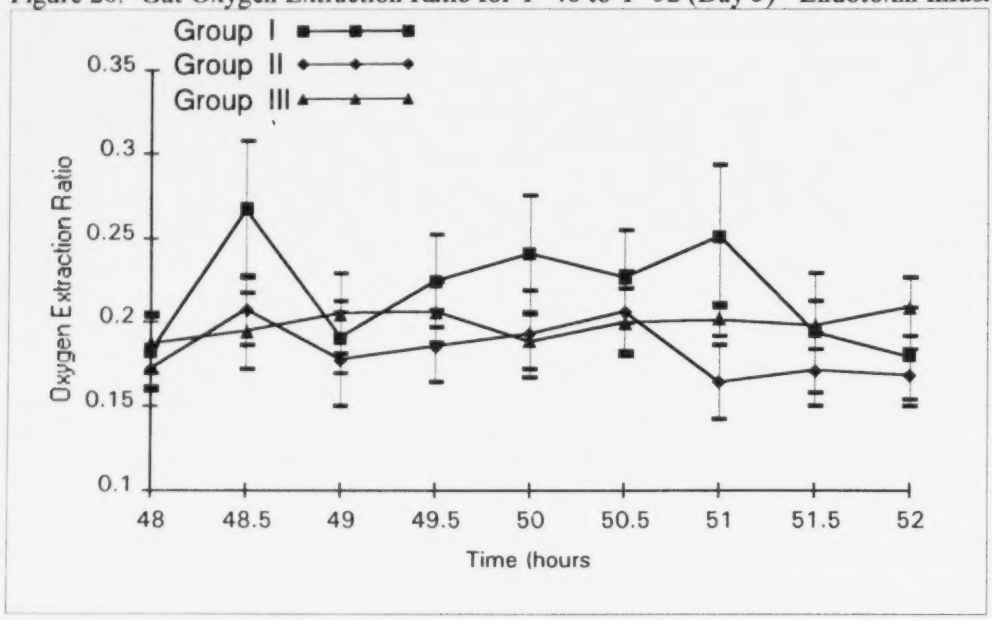


Table 113. Gut Oxygen Extraction Ratio in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	0.165	NA	NA	0.297	0.278	0.257	0.289	NA	0.145
8	0.213	0.287	0.190	0.230	0.226	0.218	0.343	0.201	0.184
14	0.116	0.135	0.123	0.132	0.124	0.140	0.099	0.103	0.100
25	0.184	0.344	0.232	0.200	0.237	0.210	0.222	0.176	0.196
26	0.235	0.303	0.217	0.262	0.338	0.308	0.303	0.294	0.271
Mean	0.183	0.267	0.191	0.224	0.241	0.227	0.251	0.194	0.179
Std.Dev.	0.046	0.091	0.048	0.063	0.079	0.062	0.096	0.079	0.064
S.E.M.	0.020	0.041	0.021	0.028	0.035	0.028	0.043	0.035	0.028

Table 114. Gut Oxygen Extraction Ratio in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	0.201	0.261	0.201	0.266	0.218	0.196	0.169	0.169	0.174
9	0.201	0.258	0.220	0.210	0.184	0.206	0.212	0.198	0.175
11	NA	0.190	0.199	NA	NA	0.200	0.101	NA	NA
29	0.191	0.247	0.126	0.168	0.153	0.175	0.158	0.145	0.147
15	0.135	0.195	0.244	0.237	0.277	0.293	0.214	0.222	0.212
17	0.164	0.146	0.099	0.127	0.158	0.157	0.137	0.120	0.140
Mean	0.173	0.207	0.178	0.186	0.193	0.206	0.164	0.171	0.168
Std.Dev.	0.029	0.046	0.062	0.048	0.058	0.052	0.049	0.047	0.033
S.E.M.	0.013	0.021	0.028	0.022	0.026	0.023	0.022	0.021	0.015

Table 115. Gut Oxygen Extraction Ratio in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	0.132	0.153	0.137	0.139	0.133	0.124	0.172	0.149	0.154
24	0.167	0.134	0.201	0.240	0.203	0.229	0.212	0.205	0.258
27	0.242	0.262	0.282	0.218	0.213	0.220	0.203	0.213	0.221
28	0.194	0.214	0.227	0.235	0.219	0.230	0.232	0.233	0.215
30	0.201	0.210	0.179	0.197	0.174	0.194	0.187	0.188	0.197
Mean	0.187	0.195	0.205	0.206	0.188	0.199	0.201	0.197	0.209
Std.Dev.	0.041	0.051	0.054	0.041	0.036	0.045	0.023	0.032	0.038
S.E.M.	0.018	0.023	0.024	0.018	0.016	0.020	0.010	0.014	0.017

P. Sigmoid Colon Mucosal Hydrogen Ion Concentration

Unexpectedly, the baseline mucosal hydrogen concentration showed a great deal of animal-to-animal variation (Table 116). This could not be explained with any degree of certainty but one possible cause is range and calibration difficulties with the blood gas analyzer machine utilized to obtain the results. This machine is designed to work on blood samples thus the saline samples from the tonometer may have been difficult for it to

interpret. Another possibility is varying degrees of gut ischemia produced by the laparotomy and placement of the flow probe around the craniomesenteric artery. In order to standardize the results obtained, they are expressed as a percent of baseline which has been done by other authors[136].

Figure 27 demonstrates the increase in mucosal [H+] seen in Group II (Table 118) and Group III (Table 119) animals. These changes are not statistically significant from Group I (Table 117). During the four hour interval, Group I animals showed no increase.

Figure 27. Sigmoid Colon Mucosal Hydrogen Ion Concentration for T=4 to T=8 (Day 1) - Hemorrhage

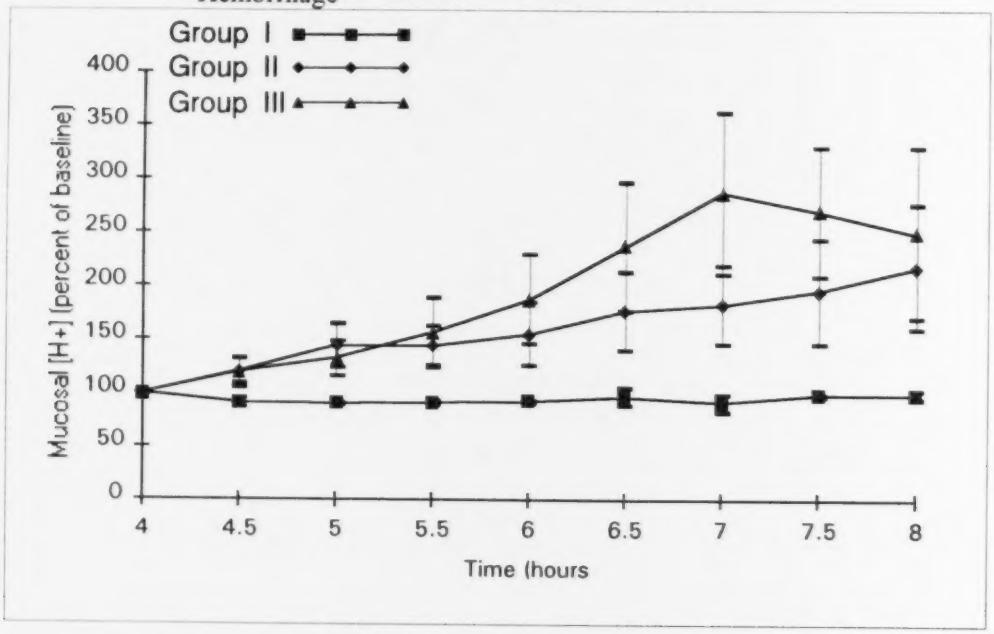


Table 116. Sigmoid Colon Mucosal Hydrogen Ion Concentration (nmol/l) for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
Group I									
25	49	46.8	44.7	45.7	45.7	51.3	49	49	50.1
26	44.7	38.9	39.8	39.8	40.7	39.8	37.2	43.7	42.7
Group II									
5	40.7	49	74.1	91.2	123	144.5	147.9	177.8	204.2
9	75.9	85.1	91.2	83.2	93.3	123	131.8	134.9	147.9
11	102.3	123	134.9	134.9	131.8	147.9	141.3	123	177.5
29	72.4	123	166	120.2	102.3	107.2	114.8	123	141.3
15	38.9	38.9	39.8	44.7	41.7	40.7	44.7	50.1	45.7
17	49	47.9	47.9	56.2	61.7	70.8	70.8	69.2	60.7
Group III									
20	52.5	87.1	91.2	125.9	162.2	213.8	263	204.2	169.8
24	53.7	49	49	50.1	58.9	57.5	70.7	70.8	7.24
27	72.4	95.5	95.5	97.8	120.2	144.5	199.5	229.1	208.9
28	57.5	58.9	58.9	49	55	70.8	69.2	70.8	81.3
30	44.7	46.8	72.4	102.3	114.8	154.9	182	173.8	213.8

Table 117. Sigmoid Colon Mucosal Hydrogen Ion Concentration (as percent of baseline) in Group I Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
25	100	96	91	93	93	105	100	100	102
26	100	87	89	89	91	89	83	98	96
Mean	100	91	90	91	92	97	92	99	99
Std.Dev.	0	6.0	1.6	3.0	1.6	11.1	11.9	1.6	4.8
S.E.M.	0	4.2	1.1	2.1	1.1	7.8	8.4	1.1	3.4

Table 118. Sigmoid Colon Mucosal Hydrogen Ion Concentration (as percent of baseline) in Group II Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
5	100	120.4	182.1	224.1	302.2	355.0	363.4	436.9	501.7
9	100	112.1	120.2	109.6	122.9	162.1	173.6	177.7	194.9
11	100	120.2	131.9	131.9	128.8	144.6	138.1	120.2	173.5
29	100	169.9	229.3	166.0	141.3	148.1	158.6	169.9	195.2
15	100	100.0	102.3	114.9	107.2	104.6	114.9	128.8	117.5
17	100	97.8	97.8	114.7	125.9	144.5	144.5	141.2	123.9
Mean	100	120.1	143.9	143.5	154.7	176.5	182.2	195.8	217.8
Std.Dev.	0	26.3	51.6	44.6	73.1	89.6	90.9	120.2	143.2
S.E.M.	0	10.7	21.1	18.2	29.8	36.6	37.1	49.1	58.5

Table 119. Sigmoid Colon Mucosal Hydrogen Ion Concentration (as percent of baseline) in Group III Animals for T=4 to T=8 (Day 1) - Hemorrhage

Pig #	Time								
	4	4.5	5	5.5	6	6.5	7	7.5	8
20	100	165.9	174	239.8	309	407.2	501	389.0	323
24	100	91.2	91.2	93.3	109.7	107.1	131.7	131.8	13.5
27	100	131.9	131.9	135.1	166.0	199.6	275.6	316.4	288.5
28	100	102.4	102.4	85.2	95.7	123.1	120.3	123.1	141.4
30	100	104.7	162.0	228.9	256.8	346.5	407.2	388.8	478.3
Mean	100	119.2	132.3	156.5	187.4	236.7	287.1	269.8	249.0
Std.Dev.	0	30.1	36.0	73.7	92.9	134.4	167.5	133.3	178.0
S.E.M.	0	13.4	16.1	32.9	41.5	60.1	74.9	59.6	79.6

On Day 3, animals in Group I (Table 121) and Group II (Table 122) both demonstrated steady elevations of mucosal [H+] over the four hour endotoxic shock (Figure 28). The rise was, however, greater in the Group II animals which had previously experienced hemorrhagic shock (not consistently statistically significant). Group I animals went up to a level of 133±33 % of baseline at T=52, while Group II animals increased to 152±28 % of baseline ($p < 0.05$ compared to Group III in both cases).

Figure 28. Sigmoid Colon Mucosal Hydrogen Ion Concentration for T=48 to T=52 (Day 3) - Endotoxin Infusion

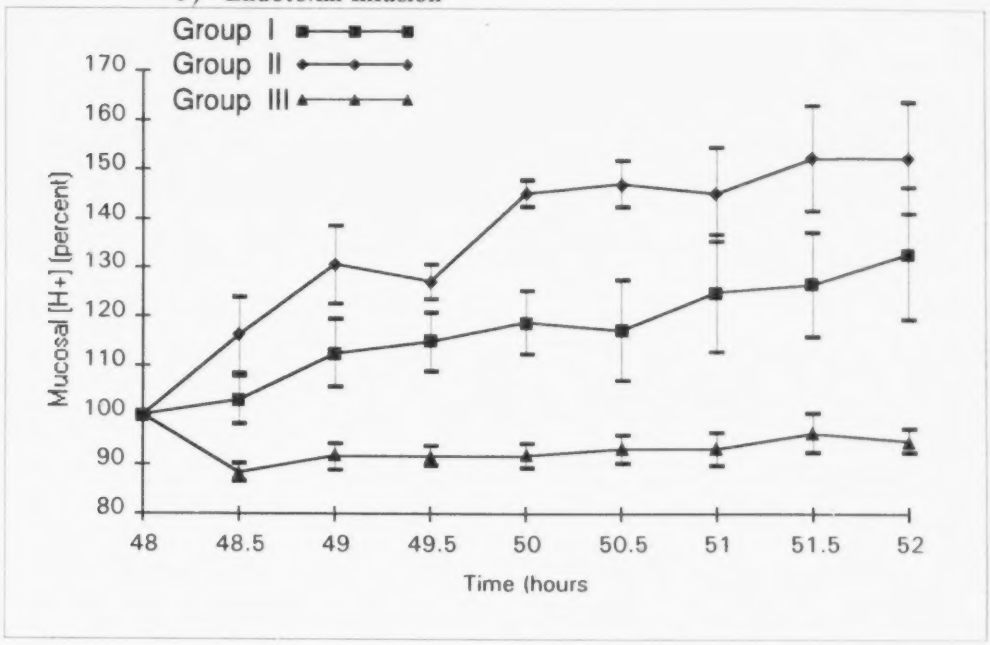


Table 120. Sigmoid Colon Mucosal Hydrogen Ion Concentration (nmol/l) for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
Group I									
7	95.4	81.3	107.2	112.2	100	97.7	102.3	107.1	151.4
8	57.5	60.3	51.3	51.3	56.2	47.9	44.7	49	40.7
10	177.8	166	186.2	199.5	218.8	223.9	229.1	251.2	269.2
14	37.2	38	38.9	47.9	50.1	55	57.5	58.9	56.2
25	41.7	47.9	56.2	46.8	49	42.7	52.5	50.1	50.1
26	39.8	46.8	51.3	51.3	53.7	56.2	61.7	56.2	57.5
Group II									
5	52.5	60.3	64.6	69.2	74.1	77.6	81.3	77.6	67.6
9	40.7	49	56.2	55	58.9	57.5	58.9	64.6	70.8
11	36.3	46.8	50.1	41.7	51.3	51.3	41.7	46.8	50.1
29	35.5	37.2	41.7	41.7	56.2	60.3	61.7	66.1	60.3
15	37.2	52.5	60.3	49	52.5	53.7	60.3	64.6	69.2
17	38.9	33.9	40.7	51.3	56.2	53.7	46.8	45.7	45.7
Group III									
20	70.8	61.7	63.1	63.1	60.3	64.6	61.7	58.9	66.1
24	41.7	34.7	37.2	39.8	36.3	36.3	38	39.8	38.9
27	41.7	38.9	39.8	40.7	40.7	42.7	39.8	43.7	42.7
28	47.90	43.70	40.70	41.70	46.80	42.70	41.70	44.70	41.70
30	51.30	44.70	51.30	45.70	46.80	49.00	53.70	53.70	50.10

Table 121. Sigmoid Colon Mucosal Hydrogen Ion Concentration (percent of baseline) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	100	85.2	112.4	117.6	104.8	102.4	107.2	112.3	158.7
8	100	104.9	89.2	89.2	97.7	83.3	77.7	85.2	70.8
10	100	93.4	104.7	112.2	123.1	125.9	128.9	141.3	151.4
14	100	102.2	104.6	128.8	134.7	147.8	154.6	158.3	151.1
25	100	114.9	134.8	112.2	117.5	102.4	125.9	120.1	120.1
26	100	117.6	128.9	128.9	134.9	141.2	155.0	141.2	144.5
Mean	100	103.0	112.4	114.8	118.8	117.2	124.9	126.4	132.8
Std.Dev.	0	12.4	16.9	14.6	15.3	25.2	29.5	26.1	33.1
S.E.M.	0	5.1	6.9	6.0	6.2	10.3	12.0	10.6	13.5

Table 122. Sigmoid Colon Mucosal Hydrogen Ion Concentration (percent of baseline) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	100	114.9	123.0	131.8	141.1	147.8	154.9	147.8	128.8
9	100	120.4	138.1	135.1	144.7	141.3	144.7	158.7	174.0
11	100.0	128.9	138.0	114.9	141.3	141.3	114.9	128.9	138.0
29	100.0	104.8	117.5	117.5	158.3	169.9	173.8	186.2	169.9
15	100.0	141.1	162.1	131.7	141.1	144.4	162.1	173.7	186.0
17	100.0	87.1	104.6	131.9	144.5	138.0	120.3	117.5	117.5
Mean	100.0	116.2	130.6	127.1	145.2	147.1	145.1	152.1	152.3
Std.Dev.	0.0	18.9	20.0	8.6	6.6	11.6	23.4	26.2	27.9
S.E.M.	0.0	7.7	8.2	3.5	2.7	4.7	9.6	10.7	11.4

Table 123. Sigmoid Colon Mucosal Hydrogen Ion Concentration (percent of baseline) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	100	87.1	89.1	89.1	85.2	91.2	87.1	83.2	93.4
24	100	83.2	89.2	95.4	87.1	87.1	91.1	95.4	93.3
27	100	93.3	95.4	97.6	97.6	102.4	95.4	104.8	102.4
29	100	91.2	85.0	87.1	97.7	89.1	87.1	93.3	87.1
30	100	87.1	100.0	89.1	91.2	95.5	104.7	104.7	97.7
Mean	100	88.4	91.7	91.7	91.8	93.1	93.1	96.3	94.8
Std.Dev.	0	3.9	5.9	4.6	5.8	6.1	7.3	9.0	5.7
S.E.M.	0	1.8	2.7	2.0	2.6	2.7	3.3	4.0	2.6

Q. Serum Endotoxin Level

Results of arterial endotoxin levels (Endotoxin Units/l) are depicted graphically in Figure 29. During the T=48 to T=52 time period, this measure was seen to rise from trace levels in Group I animals (Table 124) to a fairly steady plateau level for the remainder of the experimental run. In Group II animals (Table 125), a similar rise was seen, but to a greater peak level (14.3±10 EU/l) after the first thirty minutes. While the differences between Groups I and II, and between Groups I and III were not statistically significant at T=48.5 , Groups II and III were ($p < 0.01$). This held true for the balance of the four hour run. Control animals of Group III (Table 126) had constant trace levels. All animals in Groups I and II received the same dose of endotoxin (25 mcg/kg).

Figure 29. Serum Endotoxin Level for T=48 to T=52 (Day 3) - Endotoxin Infusion

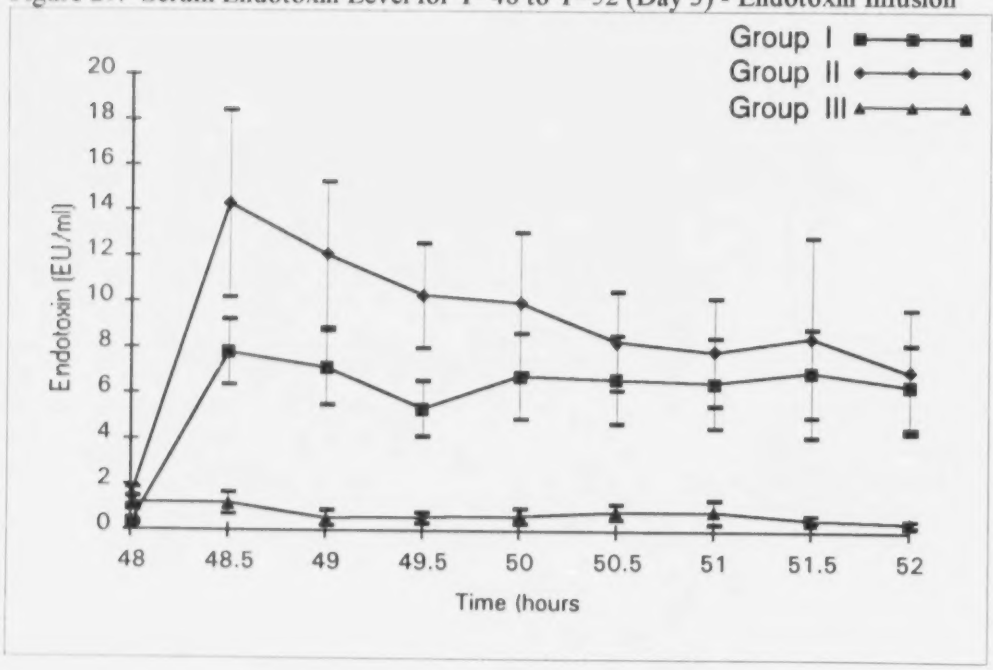


Table 124. Serum Endotoxin Level (Endotoxin Units) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	0.2	7.7	6.7	5.8	6.43	7.05	5.25	8.06	7.7
8	0.1	4.93	6.65	6.65	7.4	5.78	6.65	6.43	5.88
10	0.04	7.5	7.12	6.33	3.4	3.43	3.45	3.46	2.83
14	0.6	3.28	0.55	0.9	0.3	0.18	0.2	0.295	0.22
25	0.46	13.2	9.6	3.26	11.04	13.26	9.5	13.2	9.22
26	0.4	10.06	12.2	9.2	12.16	10.18	13.94	10.38	12.46
Mean	0.30	7.78	7.14	5.36	6.79	6.65	6.50	6.97	6.39
Std.Dev.	0.22	3.55	3.89	2.89	4.49	4.68	4.79	4.66	4.42
S.E.M.	0.09	1.45	1.59	1.18	1.83	1.91	1.96	1.90	1.80

Table 125. Serum Endotoxin Level (Endotoxin Units) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	0.73	3.9	5.85	7.05	6.63	6.83	7.25	5.85	5.78
9	0.78	24.8	16.2	16.2	11.8	8.64	4.8	4	2.9
11	0.42	3.4	4.18	3.4	3.4	3.23	4.25	3.15	4.2
29	2.26	10.06	10.06	10.84	9.2	9.6	7.24	6.32	9.64
15	1.72	26.4	10.6	6.58	4.86	3.78	4.4	1.75	0.57
17	2.84	17.2	25.6	17.72	24	17.72	19.2	29.88	18.88
Mean	1.46	14.29	12.08	10.30	9.98	8.30	7.86	8.49	7.00
Std.Dev.	0.97	10.10	7.84	5.70	7.50	5.27	5.72	10.61	6.57
S.E.M.	0.40	4.12	3.20	2.33	3.06	2.15	2.34	4.33	2.68

Table 126. Serum Endotoxin Level (Endotoxin Units) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	1	0.43	0.2	0.18	0.18	0.43	0.17	0.62	0.17
24	0.84	0.56	0	0	0	0.4	0	0	0
27	0.38	0.5	0	1.22	0.48	1.24	2.9	0.86	0.5
28	2	2.88	1.6	0.84	1.6	0.36	0.8	0.84	0.48
30	1.8	1.7	1.06	0.8	1.1	1.9	0.54	0.4	0.88
Mean	1.20	1.21	0.57	0.61	0.67	0.87	0.88	0.54	0.41
Std.Dev.	0.68	1.07	0.72	0.50	0.67	0.68	1.17	0.36	0.34
S.E.M.	0.30	0.48	0.32	0.23	0.30	0.31	0.52	0.16	0.15

R. Serum Lactate Level

All animals began at T=48 with similar baseline lactate levels. Over the Day 3 experimental period, Group I animals (Table 127) demonstrated a slow, steady rise in lactate concentration from 9.12±3.7 to 25.8±22.8 mg/dl at T=52. Most of this rise, and the large standard deviation is attributable to animal 10, which had a much greater increase in lactate than the other animals in this group. Most of these animals showed a recovery with lactate levels falling after two hours. Group II animals (Table 128), had a greater rise in lactate levels from 8.35±1.73 to 32.96±9.3 and 27.8±14.8 mg/dl at T=50 and T=52 respectively. This was statistically different from Group III (Table 129) at times from T=48.5 to T=52 ($p < 0.001$). Group II showed significant difference ($p < 0.01$) from Group I at T=49 to T=50. Group III animals remained near baseline.

Figure 30. Serum Lactate Level for T=48 to T=52 (Day 3) - Endotoxin Infusion

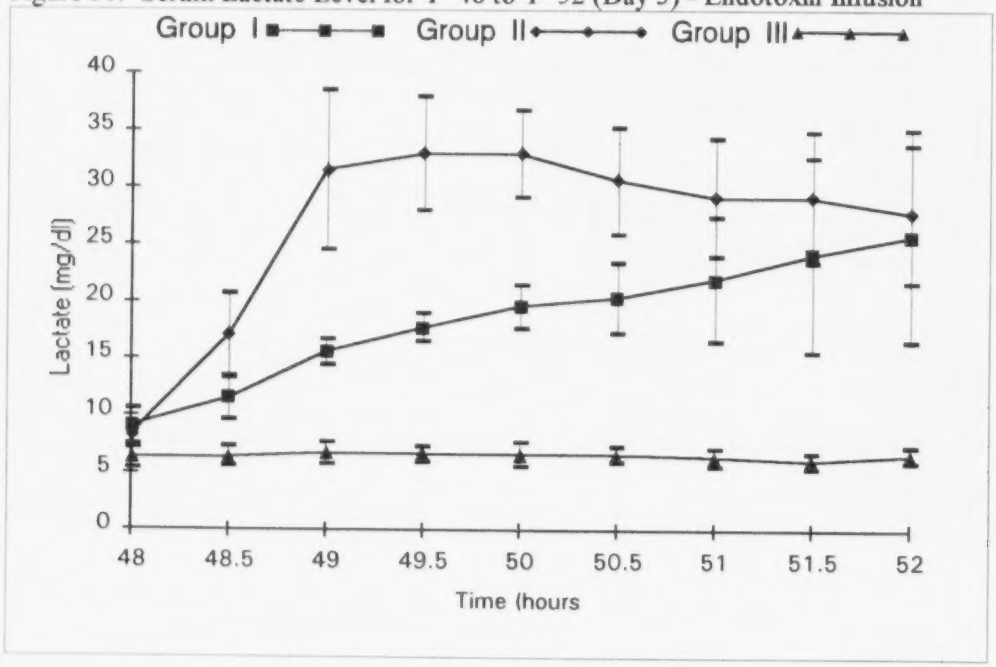


Table 127. Serum Lactate Level (mg/dl) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	6.36	6.90	12.56	13.28	13.18	11.31	11.78	14.37	20.7
8	9.22	18.29	19.97	16.69	17.64	16.11	15.06	15.09	16.29
10	5.08	9.10	12.41	16.77	21.08	31.23	48.17	66.95	71.87
14	14.49	11.67	15.31	22.02	27.45	27.18	22.45	18.15	16.75
25	7.25	8.25	16.82	18.95	18.11	16.67	15.10	13.53	13.43
26	12.34	14.82	16.64	18.98	20.55	20.03	19.4	16.64	15.59
Mean	9.12	11.51	15.62	17.78	19.67	20.42	21.99	24.12	25.77
Std.Dev.	3.65	4.35	2.87	2.94	4.73	7.46	13.36	21.05	22.71
S.E.M.	1.49	1.78	1.17	1.20	1.93	3.05	5.45	8.59	9.27

Table 128. Serum Lactate Level (mg/dl) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	7.43	12.03	24.43	26.68	29.06	32.81	30.35	27.46	24.74
9	6.22	13.13	24.22	36.52	39.47	32.28	35.34	46.52	49.56
11	11.41	30.39	51.94	49.88	47.98	51.87	50.86	46.16	41.24
29	8.54	12.01	17.87	19.82	22.81	19.53	17.23	13.53	11.7
15	8.57	26.15	54.51	42.91	32.23	22.64	17.85	17.67	15.47
17	7.95	8.79	16.33	21.94	26.22	24.74	23.32	23.47	24.1
Mean	8.35	17.08	31.55	32.96	32.96	30.65	29.16	29.14	27.80
Std.Dev.	1.73	8.89	17.12	12.10	9.30	11.66	12.77	14.16	14.75
S.E.M.	0.71	3.63	6.99	4.94	3.80	4.76	5.21	5.78	6.02

Table 129. Serum Lactate Level (mg/dl) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	4.09	4.49	4.58	5.17	4.91	6.17	5.26	4.58	4.81
24	4.55	4.31	4.83	5.26	5.74	5.67	5.79	5.66	5.98
27	7.17	7.99	7.82	7.31	5.20	5.80	5.69	5.77	7.64
28	8.34	7.05	6.88	6.92	7.11	6.58	5.94	6.36	6.09
30	7.64	8.27	9.76	8.92	10.47	9.09	9.56	8.32	8.63
Mean	6.36	6.42	6.77	6.72	6.69	6.66	6.45	6.14	6.63
Std.Dev.	1.91	1.90	2.16	1.56	2.28	1.40	1.76	1.38	1.50
S.E.M.	0.86	0.85	0.96	0.70	1.02	0.63	0.79	0.62	0.67

S. Serum Glucose Level

Glucose levels were measured regularly over the four hours on Day 3 and are graphed below (Figure 31). Group I (Table 130) showed an initial rise over the first hour (from 78.8±15 to 96.5±30 mg/dl at T=49) before falling off to a subnormal level. Group II animals (Table 131) experienced a greater degree of initial increase in glucose level (79.1±19 to 117±35 mg/dl at T=48.5) than did Group I. This was significantly different from both of the other groups ($p < 0.05$). Group III animals (Table 132) remained near baseline levels throughout the four hour period.

Figure 31. Serum Glucose Level for T=48 to T=52 (Day 3) - Endotoxin Infusion

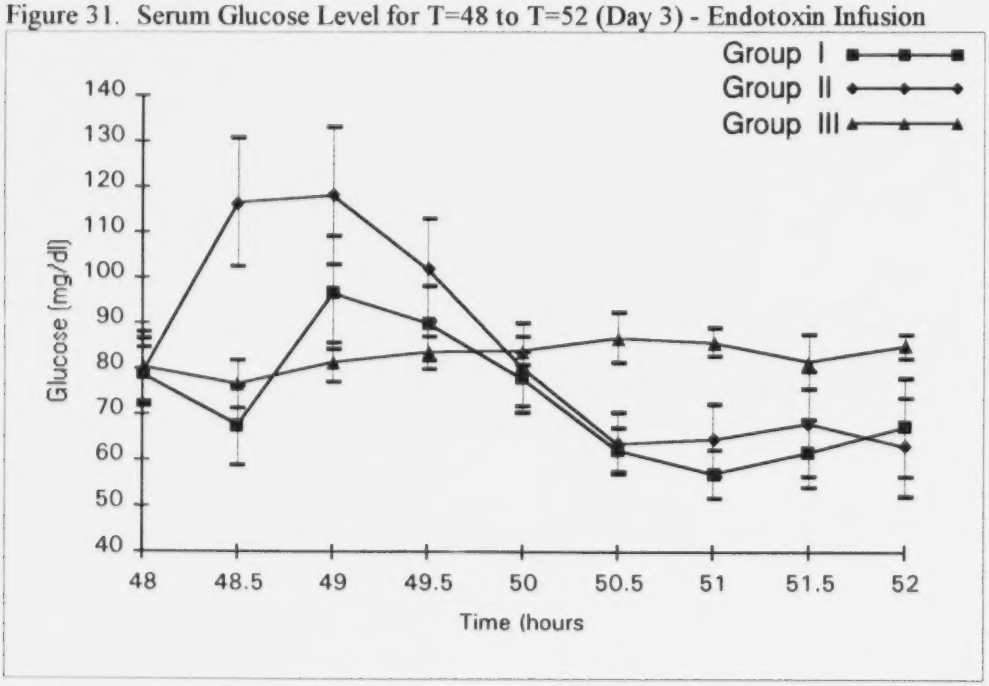


Table 130. Serum Glucose Level (mg/dl) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	95	42	45	55	54	54	62	82	100
8	94	92	98	92	76	64	59	61	64
10	83	45	108	109	78	52	46	56	63
14	56	66	84	87	101	84	78	85	97
25	73	73	136	86	75	60	43	42	44
26	72	88	108	111	83	59	54	44	36
Mean	79	68	97	90	78	62	57	62	67
Std.Dev.	15	21	30	20	15	12	13	18	26
S.E.M.	6	9	12	8	6	5	5	8	11

Table 131. Serum Glucose Level (mg/dl) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	103	102	98	105	94	73	88	102	84
9	91	102	126	142	112	83	77	83	89
11	53	128	96	61	46	48	50	44	47
15	76	182	190	120	90	78	79	88	85
17	88	87	106	94	76	53	54	61	45
29	64	98	92	89	63	46	39	30	28
Mean	79	117	118	102	80	64	65	68	63
Std.Dev.	19	35	37	28	24	16	19	28	26
S.E.M.	8	14	15	11	10	7	8	11	11

Table 132. Serum Glucose Level (mg/dl) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	109	90	90	97	93	105	93	88	89
24	75	78	82	84	85	86	88	86	88
27	80	83	91	82	85	88	84	83	86
28	64	59	69	81	83	84	89	92	87
30	74	73	75	74	74	71	75	59	75
Mean	80	77	81	87	84	87	86	82	85
Std.Dev.	17	12	10	8	7	12	7	13	6
S.E.M.	8	5	4	4	3	5	3	6	3

T. Serum Cortisol Level

Both Group I (Table 133) and Group II (Table 134) animals demonstrated a steady rise in serum cortisol level over the four hours of endotoxic shock (ANOVA $p < 0.005$ for both groups). There was no discernable difference between the two groups with respect to this rise (Figure 32) but both groups were statistically different from Group III at both T=48.5 ($p < 0.01$) and T=52 ($p < 0.001$). Data was not obtained from two of the animals from Group II due to sampling error. Group III animals (Table 135) maintained near-baseline cortisol levels.

Figure 32. Serum Cortisol Level for T=48 to T=52 (Day 3) - Endotoxin Infusion

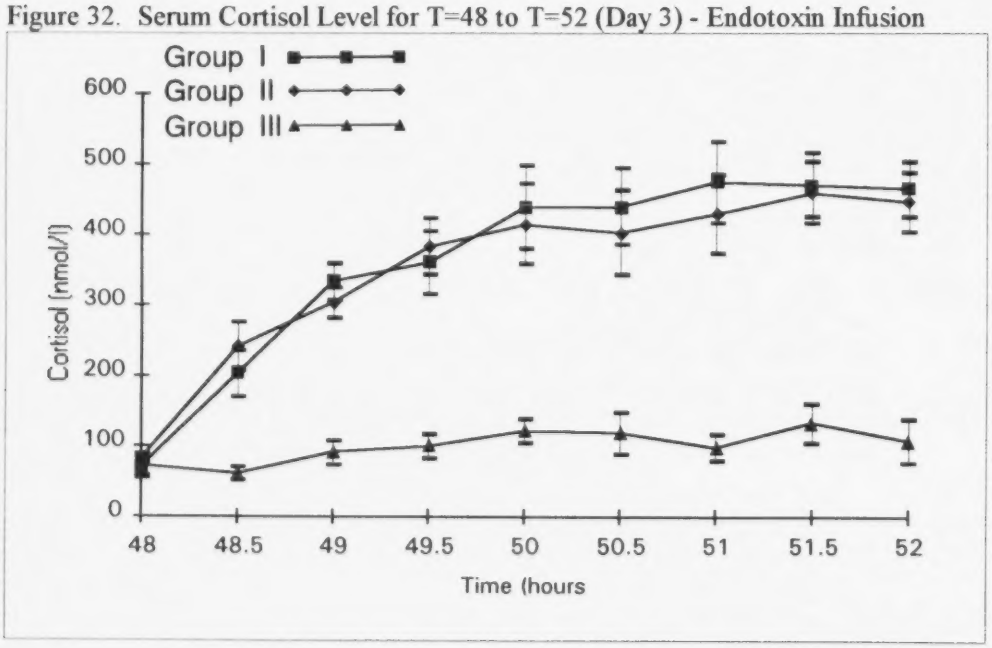


Table 133. Serum Cortisol Level (nmol/l) in Group I Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
7	NA	NA	NA	NA	NA	NA	NA	NA	NA
8	NA	NA	NA	NA	NA	NA	NA	NA	NA
10	40	115	270	304	351	341	340	413	404
14	108	266	368	348	472	470	478	401	426
25	60	231	311	303	347	371	466	477	460
26	81	202	385	489	588	579	618	596	576
Mean	72	204	334	361	440	440	476	472	467
Std.Dev.	29	65	53	88	115	108	114	89	77
S.E.M.	15	32	26	44	57	54	57	45	38

Table 134. Serum Cortisol Level (nmol/l) in Group II Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
5	104	262	326	430	458	472	496	483	496
9	85	77	258	278	176	140	205	391	400
11	62	288	369	423	443	439	470	467	494
29	82	251	243	271	350	330	326	304	309
15	89	326	278	523	586	546	582	618	596
17	79	240	348	375	478	495	502	498	391
Mean	84	241	303	383	415	404	430	460	448
Std.Dev.	14	86	51	97	139	148	138	106	101
S.E.M.	6	35	21	40	57	60	56	43	41

Table 135. Serum Cortisol Level (nmol/l) in Group III Animals for T=48 to T=52 (Day 3) - Endotoxin Infusion

Pig #	Time								
	48	48.5	49	49.5	50	50.5	51	51.5	52
20	95	40	84	63	138	182	95	65	78
24	134	90	138	167	178	76	82	161	76
27	40	56	119	94	106	112	116	95	71
28	54	40	40	88	75	41	46	124	89
30	40	79	78	90	114	186	154	225	227
Mean	73	61	92	100	122	119	99	134	108
Std.Dev.	41	23	38	39	38	64	40	62	67
S.E.M.	18	10	17	18	17	29	18	28	30

IV. Bacteriology Results

Tissue and blood culture results are reported in the following tables. All positive cultures are identified with those cultures considered to be representing translocated enteric bacteria emphasized by ***italics and underlining***. Specimens showing no growth after 5 days are indicated as **NG**. Specimens not available are indicated as **NA**.

Due to the fact that the animals had indwelling catheters in place for 5 days, typically skin-derived bacteria were disregarded and considered as contaminants. Furthermore, because the animals underwent orotracheal intubation on two occasions, oropharyngeal and upper respiratory flora were ruled out as contaminants. The decision as to what constituted a common gut organism or contaminant was based on several criteria. The first was through a review of the literature[198,199,200] as well as Dr. G. Gelfand's thesis of 1989. The second was through discussion with the microbiologist who characterized the bacteria (Dr. J.A. Talbot - University of Alberta, Department of Medical Microbiology). Common intestinal microflora of the swine cultured are given (Table 136) as are the contaminants encountered (Table 137).

Table 136. Bacteria Considered Common Enteric Organisms

Enterococcus	***Ecc***
Escherichia coli	***Ec***
Clostridium perfringens	***Clp***
Enterobacter cloacae	***Ebc***
Klebsiella sp.	***Klb***

Table 137. Bacteria Considered Contaminants

Coagulase Negative Staphylococci	CNS
Staphylococcus aureus	SA
Streptococcus viridans	SV
Diptheroids	DIP
Beta hemolytic Streptococcus	BHS
Pasteurella multocida	PM
Lactobacillus	LB
non-perfringens Clostridium sp.	CNP
Anaerobic gram positive cocci	AGPC
Anaerobic gram positive bacilli	AGPB
Anaerobic gram negative bacilli	ABNB

A. Blood Cultures

Blood was cultured from animals at 12 hour intervals throughout the experiment. No pathogens were seen in cultures obtained from T=0 to T=48 in any groups. After this time, 6 cultures from Group II animals (in 3 different animals) grew pathogens ($p < 0.01$) while none were seen in cultures from other groups. Contaminants were infrequent and invariably transient.

Table 138. Organisms Isolated from Systemic Blood of Group I Animals

Pig #	Time								
	0	12	24	36	48	60	72	84	96
7	NG	NG	NG	NG	DIP	PM	NG	NG	NG
8	NA	NG	NG	NG	NG	NG	CNS	CNS SA	CNS
10	NA	NA	NA	NA	NA	PM	NG	NG	NG
14	NA	NG	NG	NG	NG	NG	CNS	NG	NG
25	NG	NG	NG	NG	NG	NG	NG	NG	NG
26	NG	NG	NG	NG	NG	NG	NG	NG	NG

Table 139. Organisms Isolated from Systemic Blood of Group II Animals

Pig #	Time								
	0	12	24	36	48	60	72	84	96
5	NG	NG	NG	NG	NG	NG	NG	NG	NG
9	NA	NG	NG	NG	NG	NG	NG	NG	CNS ***Ecc***
11	NA	NG	NG	NG	NG	NG	NG	***Clp***	NG
29	NG	NG	NG	NG	SA	NG	NG	NG	NG
15	NG	NG	NG	NG	NG	NG	NG	NG	CNS
17	NG	NG	SA	NG	NG	***Ebc***	***Ebc***	***Ebc***	***Ebc***

Table 140. Organisms Isolated from Systemic Blood of Group III Animals

Pig #	Time								
	0	12	24	36	48	60	72	84	96
20	NG	NG	NG	NG	NG	NG	NG	NG	NG
24	NG	NG	NG	NG	NG	NG	NG	NG	NG
27	NG	NG	NG	NG	NG	NG	NG	CNS SA	NG
28	CNS	NG	NG	NG	NG	NG	NG	NG	CNS
30	NG	NG	NG	NG	NG	NG	NG	NG	NG

Table 141. Summary of Arterial Blood Cultures

Result	Group I	Group II	Group III
Positive	0	6	0
Negative	47	46	45
Total (Contaminant)	47 (7)	52 (4)	45 (3)

B. Lymph Nodes

As has been seen in all studies of bacterial translocation, mesenteric lymph nodes are almost invariably infected. Emphasis should not be placed on these results as bacteria present in lymph nodes are often in the process of being destroyed by normal immunologic processes. It was surprising, however, that nodes in Group III (Table 144) had not cleared themselves of bacteria by T=96 as this was 4 days after the hemorrhagic shock. Possibly the anaesthetic which they underwent on Day 3 was a stress sufficient enough to prevent effective destruction of bacteria translocated to these nodes. The number of animals with pathogens in nodes, and the total number of nodes involved, were not significantly different among the groups. It is, however, noteworthy that 2 of the Group II animals (Table 143), had *Enterococcus* in lymph nodes which was not seen in animals in the other groups.

Table 142. Organisms Isolated From Lymph Node Cultures (taken at T=96) of Group I Animals

Pig #	Lymph Node		
	1	2	3
7	CNS ***Ec***	***Ec***	***Ec***
8	CNS ***Ec***	***Ec***	CNS
10	NG	CNS BHS ***Ec***	NG
14	SA AGNB ***Ec***	CNS SA	SA SV AGNB ***Ec***
25	CNS ***Ec***	CNS ***Ec***	***Ec***
26	SA ***Ec***	CNS ***Ec***	LB

Table 143. Organisms Isolated From Lymph Node Cultures (taken at T=96) of Group II Animals

Pig #	Lymph Node		
	1	2	3
5	*Ec*	CNS *Ecc* *Ec*	CNS
9	CNS BHS	CNS *Ec* *Klb*	*Ec*
11	CNS	*Ec* *Ecc*	CNS
29	*Ec*	*Ec*	CNS *Ec*
15	CNS SA *Ec*	CNS SA *Ec*	*Ec*
17	CNS SA *Ec*	CNS SA *Ec*	CNS SA *Ec*

Table 144. Organisms Isolated From Lymph Node Cultures (taken at T=96) of Group III Animals

Pig #	Lymph Node		
	1	2	3
20	CNP	*Ec*	NG
24	SA AGPC *Ec*	SA AGPC *Ec*	AGPC *Ec*
27	CNS	CNS SA *Ec*	CNS SA
28	CNS SV	NG	CNS SA
30	*Ec*	*Ec*	CNS SA AGNB *Ec*

Table 145. Summary of Lymph Node Tissue Cultures

Result	Group I	Group II	Group III
Positive	13	14	8
Negative	5	4	7
Total (Contaminant)	18 (12)	18 (12)	15 (10)

C. Solid Organs

The presence of bacteria in parenchymal organs is likely of great significance in a model of surgical infection. Clinically, infection that does not spread to the systemic circulation is rarely detected but doubtless plays an important role in sustaining activation of cytokines and bringing about organ failure. In Group I (Table 146), 1 animal of 6 had a positive organ culture while in Group II (Table 147), this was seen in 5 of the 6 animals. In Group III (Table 148), 3 of 5 animals has a positive tissue culture suggesting that the hemorrhagic shock, followed by a period of anaesthesia on Day 3, was sufficient to allow some enteric bacteria to proceed beyond MLNs. In Group I, only 1 of 24 organs sampled was positive while in Group II, 10 of 24 were positive, and 4 of 20 in Group III. In this respect, the difference between Groups I and II, and Groups II and III were statistically significant ($p < 0.01$ and $p < 0.05$ respectively). Groups I and III were not significantly different. Again, *Enterococcus* was seen in 4 of the 6 Group II animals while neither of the other groups' cultures grew this type of bacteria. It should be noted that while 4 of these animals has positive tissue culture for *Enterococcus*, only 1 had *Enterococcus* in a blood culture, thus there is demonstrated tissue sepsis involving a pathogen without this pathogen being detectable in the blood.

Table 146. Organisms Isolated from Tissue Cultures (taken at T=96) of Group I Animals

Pig #	Lung	Liver	Spleen	Kidney
7	CNS	CNS	CNS	CNS
8	NG	CNS SA	CNS	CNS SA
10	PM SV BHS LB AGPB	CNS BHS	CNS BHS ***Ec***	CNS BHS
14	SA	CNS SA CNP	CNS SA	CNS SA CNP
25	CNS	CNS SV	CNS	CNS SA
26	CNS SV	CNS SA	CNS SA SV	CNS SA

Table 147. Organisms Isolated from Tissue Cultures (taken at T=96) of Group II Animals

Pig #	Lung	Liver	Spleen	Kidney
5	CNS	CNS SA ***Ecc***	CNS	NG
9	CNS	CNS BHS ***Ecc***	CNS ***Ecc***	CNS BHS
11	CNS ***Ecc*** ***Clp***	CNS	CNS ***Clp***	CNS ***Ecc*** ***Clp***
29	SV	CNS	CNS ***Ec***	CNS
15	CNS SA	CNS SA SV	CNS SA	CNS SA
17	CNS SV	CNS SA ***Ecc***	CNS ***Ec***	CNS SA ***Ec***

Table 148. Organisms Isolated from Tissue Cultures of Group III Animals

Pig #	Lung	Liver	Spleen	Kidney
20	CNS SA PM	CNS SV	CNS	CNS SV
24	SA	CNS SA AGPC AGNB	CNS SA *Ec*	SA *Ec*
27	NG	CNS SA	CNS SA	CNS SA
28	CNS	CNS SV	CNS SV	SA SV *Clp*
30	CNS SA	CNS SA *Ec*	CNS	CNS

Table 149. Summary of Solid Organ Tissue Cultures

Result	Group I	Group II	Group III
Positive	1	10	4
Negative	23	14	16
Total (Contaminant)	24 (23)	24 (23)	20 (19)

Considering the positive cultures by organ (Table 150), we see that the spleen is most frequently involved.

Table 150. Incidence of Positive Tissue Cultures by Organ

Organ	Group I	Group II	Group III
Lung	0/6	1/6	0/5
Liver	0/6	3/6	1/5
Spleen	1/6	4/6	1/5
Kidney	0/6	2/6	2/5
Total	1/24	10/24	4/20

Polymicrobial infection has been suggested to be of significance in causing increased morbidity due to organ failure[201]. In this experiment, only animals that received two sequential physiologic insults (Group II) developed a detectable polymicrobial infection.

Table 151. Summary of Culture Specimens Positive for Polymicrobial Infection (> 1 Pathogen)

Specimen	Group I	Group II	Group III
Blood	0	0	0
Lymph Node	0	3	0
Lung	0	1	0
Liver	0	0	0
Spleen	0	0	0
Kidney	0	1	0
Total	0	5	0

DISCUSSION

The gut hypothesis of multiple system organ failure is recognized by virtually all who are familiar with this syndrome. Although the exact mechanism by which bacteria and toxins pass from the gastrointestinal tract remains controversial, most agree that the gut plays an active role in the initiation and perpetuation of the malignant systemic inflammatory response that characterizes this condition. It has been the purpose of this study to investigate the translocation of gut bacteria to normally sterile sites in response to non-infectious stresses. In particular, the response to a delayed second stressor has been examined with respect to bacterial translocation, hemodynamic changes, and select biochemical measures.

I. Experimental Design

From previous research, we know that detectable bacterial translocation after hemorrhagic shock is not an acute event in swine, and that seven hours after a sub-lethal hemorrhage, gut bacteria cannot be cultured even from mesenteric lymph nodes[51] which are generally the first site to demonstrate translocated gut flora. Other authors have found that 96 hours after a systemic stress, in the absence of an additional insult, most translocated bacteria were cleared from the lymph nodes and organs[40]. Bacterial translocation to MLN in pigs has been most consistantly demonstrated at 48 hours after a physiologic insult[40,48,60]. Therefore, in this study, the 'second hit' was administered 48 hours after the first insult, at a time when it could be reasonable assumed that bacteria would be in MLNs and the animal's inflammatory mediator system would be 'primed'.

Tissue cultures were taken 48 hours later (96 hours total) in order to allow any bacterial effects of the second insult to take effect.

Hemorrhagic shock is an easily reproducible physiologic insult. It is also very commonly the initial stressor encountered by a traumatized human. A Wigger's - type model of shock[202] was chosen in which a steady subnormal mean arterial pressure (MAP) is attained by hemorrhage into a reservoir, and maintained by further blood removal or re-infusion as necessary. Based on previous work in our laboratory[51,158] and by others[155,203], animals were bled to a MAP of 40 mmHg and maintained at that level for four hours before reinfusion with shed blood, and crystalloid, as necessary to return to pre-shock MAP. Although this shock is more severe than is commonly seen in critically ill and traumatized patients, it was felt that to maximize whatever priming effect the first stressor might have, it should be of a fairly large magnitude.

Colonization from a variety of sources (both exogenous and endogenous) is very common in critically ill patients during the first 3 days of hospitalization. Infusion of bacterial endotoxin reliably reproduces the metabolic effects of a bacterial load without actually causing infection. Using common laboratory equipment, preparation and infusion of a sterile solution of purified endotoxin is readily achieved at little expense . It is with these points in mind that endotoxic shock was chosen as the second stressor for this experiment. Although the exposure to endotoxin in critically ill patients can be gradual and over a period of many hours, in the experiment, we chose to infuse the endotoxin as a bolus (over 30 minutes) in order to achieve an observable response within a reasonable amount of time during which the animals could be anaesthetized and monitored. It was delivered by way of the portal vein primarily because this catheter was not connected to a pressure monitor. This allowed full exposure of the resident macrophages of the liver to the endotoxin. Although most experiments with endotoxemia deliver it intravenously or intraperitoneally, the response that was seen using the portal route was not identifiably

different in terms of any of the hemodynamic and biochemical parameters measured in this experiment.

The three groups of animals used in this experiment included endotoxin only (Group I), hemorrhage and endotoxin (Group II), and hemorrhage only (Group III). A point of criticism could be the absence of a control group of animals that were operated on only, and received neither hemorrhage nor endotoxin. Although such a group would add to the completeness of the study, time and financial resources were not available to make this possible. Historic controls from previous research in our laboratory[51,158] show that animals operated on and not shocked will display bacterial translocation to MLNs only after 48 hours, and will remain hemodynamically and biochemically stable during anaesthetics.

II. Swine Model

The use of animal models of human disease is essential to gaining an understanding of the dynamic, multifaceted response of a living organism to disruption of homeostasis. No model is without some disadvantages. Although working with rodents in the laboratory is much more practical in terms of handling, cost and familiarity, there are several reasons why a swine model was chosen for this project.

Over the past six years, our laboratory staff have developed a model of hemorrhagic shock in 30-40kg pigs in order to study bacterial translocation and gut function in these animals. The first study by Gelfand[51] showed that bacterial translocation

did not occur within 6 hours of hypovolemic shock in contrast to what has been shown in rodent models[14,150,156] and is therefore not an acute phenomenon in pigs. This conclusion might be extrapolated to include other large mammals such as man.

Many of the studies in rodents cite the importance of xanthine oxidase-generated free radicals in the pathogenesis of gut mucosal failure[134,137]. However, the gut concentration of xanthine oxidase in humans and in pigs is much lower than that seen in rodents[141,143,204] and therefore, the applicability of data from rodent experiments to the human state must be questioned.

Other similarities of swine to humans include gastrointestinal and cardiovascular physiology. Because swine, as opposed to rodents and dogs, are true omnivores, their gastrointestinal tract has developed with many similarities to man's. In a 30 to 40 kilogram pig, the GI tract is of a length comparable to a human's[205]. Nutrient requirements, carbohydrate metabolism, gut fermentation patterns, and insulin-glucose axis are all better matched to humans in swine than any other non-primate mammalian species[206,207]. Also, amino acid utilization and protein synthesis are much more similar to humans in pigs than in rodents[180,181,208]. Cardiovascular similarities include anatomy[205,209], resting hemodynamic values[210], a spleen with less contractile capacity than dogs, and a functional response to stress that more closely simulates humans than do dogs[209]. Thus, as a model of gut barrier function, hemodynamics, and metabolic response to sequential hemorrhagic and endotoxic shock, the pig seems well suited.

Optimally, this experiment would be carried out on a chronically instrumented, awake pig. This would both eliminate possible hemodynamic interference by the anaesthetic agents, and allow normal endogenous opiates and corticotropins[211] to have their effect as would be seen in a traumatized human.

The technical difficulties in treating and monitoring an awake 40 kg pig are great and thus it was decided to anaesthetize the animal during the shock periods as well as for surgery. Ketamine and atropine were chosen for premedication as they allow easy induction, minimize secretions, and are short acting[195]. An inhaled agent offers the simplest maintenance anaesthetic and therefore Isofluorane was chosen over Halothane which carries much greater cardiodepressive effects as well as a loss of splanchnic autoregulation[212]. Also, isofluorane is not metabolized in the liver and therefore is not likely to induce or suppress any enzymes or produce toxic metabolites[212,213]. In addition, it does not sensitize the myocardium to catecholamines which might cause arrhythmias[212,213]. With the depth of anaesthesia and shock involved with this experiment, it was also necessary to ventilate the animals as they would likely not breathe adequately on their own. Oxygenation was maintained well above normal ranges to provide a buffer against deviation of the PaO_2 into an hypoxic range. This further simulates the clinical situation in traumatized humans.

A splenectomy was not performed as part of the surgery on Day 1. This was considered initially since an intact spleen in pigs results in mobilization of sequestered red blood cells and less tachycardia during hemorrhagic shock[209]. Although these features make the porcine model slightly different from humans, the spleen was left in place because of an increase in bacterial translocation that has been observed in splenectomized mice versus sham-operated mice when endotoxin is administered[94]. This difference has been attributed to down-regulation of Kupffer cells and their release of inflammatory mediators in response to endotoxin, and to a decrease in endotoxin-induced gut mucosa histologic changes. Because of the presence of a spleen, portal blood was not exclusively of mesenteric venous origin, but also contained systemic blood from splenic outflow. In a model of pure hemorrhagic shock only, a splenectomized animal would definitely be more appropriate.

III. Hemodynamics

Although a great deal of information was gathered during the hemorrhagic shock of Day 1, the focus of this work is on the changes observed during the second insult, given on Day 3. This hemodynamic information was gathered in order to document the degree of shock attained by each group of animals and to demonstrate any differences in the response by each group to the endotoxic insult. The familiar parameters of blood pressure, heart rate, and central venous pressure were measured at regular intervals. Also, the rate of blood flow in the principle vascular conduit of the gastrointestinal tract was monitored to show how the administered shock affected the delivery of blood to the gut.

On Day 1, approximately 500 ml of blood was removed from animals in Groups II and III during the first 30 minutes in order to obtain the desired MAP. Subsequent to this, approximately 500 ml more needed to be withdrawn over the next two hours in order to maintain shock, after which time, small amounts of shed blood generally needed to be reinfused. Using this Wiggers technique[202], the MAP of the Group II and Group III animals was kept within remarkably tight control over the four hours with no deviation greater than 3 mmHg tolerated. The heart rate and central venous pressure responses to hypovolemia were as expected. It was of interest, however, that the tachycardia which developed in bled animals did not begin until approximately 30 minutes after the desired MAP of 40 mmHg was attained. This likely represents a period of compensated shock. The fall of CAF observed (in the four animals in which the flow probe coupled on Day 1) showed significant deprivation of blood flow to the gut during the hemorrhagic shock. Insignificant decreases in MAP and CVP were seen in Group I animals during their four hours of anaesthetic. This might possibly be due to ongoing fluid shifts resulting from the immediately preceding surgery.

During endotoxin infusion on Day 3, the difference between the group previously hemorrhaged (Group II), and the one that was not (Group I) was remarkable. The Group I animals displayed a transient hyperdynamic response while the Group II animals seemed unable to mount this response and simply slipped into an hypotensive state without developing a significant tachycardia. This hyperdynamic state likely resulted from the transient increase in systemic vascular resistance and pulmonary vascular resistance which has come to characterize endotoxic shock[116,135,136]. Initially, both groups of animals receiving endotoxin displayed a fall in CAF, but only the animals which had previously been in hemorrhagic shock did not recover flow within 30 minutes of the completion of endotoxin infusion. This likely represented a lowered cardiac output combined with a sustained elevation of mesenteric vascular resistance. These differences seen between the two groups receiving endotoxin could be due to an inflammatory mediatory system which has either been previously exhausted, or activated to give a greater response to the endotoxin. Another possible explanation is impaired clearance of endotoxin in the previously stressed animals. The hemodynamic values of the Group III animals remained constant during the four hours thus the changes seen in the other two groups are not simply a result of anaesthesia.

The amount of oxygen required by animals was adjusted by the investigator to maintain a state of adequate oxygenation within the prescribed parameters of PaO_2 and SaO_2. Changes were not statistically significant but a trend was noted toward higher oxygen requirements in animals receiving endotoxin on Day 3 (especially during the first two hours). This was likely due to development of pulmonary edema and pulmonary vasoconstriction which are known to develop during endotoxic states[214].

The initial weights of the groups of animals were not statistically significantly different. Also, the baseline hemodynamic values at T=4 and T=48 were not significantly different thus the groups were well matched at the onset of experimentation. After

surgery, anaesthetics and shocks, animals tended to eat and defecate in a normal manner suggesting that results were not simply due to starvation. Although food intake was not precisely monitored (due to technical difficulty), there was no subjectively observed difference in eating behavior between groups of animals.

IV. Biochemistry

A number of biochemical parameters were measured every 30 minutes during both hemorrhagic and endotoxic shock periods. These include laboratory values such as arterial and portal venous blood gases, glucose, lactate, endotoxin and cortisol, as well as calculated values of arterial and portal venous oxygen content, gut oxygen delivery and uptake. Results obtained during hemorrhagic shock will be briefly discussed, followed by results from the second hit, endotoxemia.

On Day 1, animals undergoing shock from hemorrhage displayed trends toward acidosis and loss of bicarbonate. These changes did not consistently reach statistical significance but would seem to be a reasonably predictable response to a hypovolemic stress state. Arterial blood gas results otherwise showed no significant changes over time and the experimental groups were similar in this respect. This suggests that oxygenation and ventilation were comparable among the groups.

Portal venous blood gases were sampled simultaneously with arterial blood every 30 minutes during experimentation. During hemorrhagic shock on Day 1, a significant fall in the portal venous P_aO_2 was seen in both groups of animals that were bled. These

animals also demonstrated a significant decline in S_pO_2. This suggests either a diminished delivery of oxygen to the gut, or an increased uptake. A trend was also seen toward the development of portal acidosis suggesting that demand for oxygen was greater than delivery and uptake were able to supply.

Unresuscitated hemorrhage caused a trend toward increasing hemoglobin concentration during the four hour shock period. Since no blood was given, this would suggest hemoconcentration caused by a fluid shift from the intravascular to extravascular compartment. Because this was not seen in non-hemorrhaged animals, we may assume that it was not simply a result of post-operative fluid shifts.

While the content of oxygen in arterial blood was seen to increase slightly during hemorrhage, the C_pO_2 fell significantly. Combining these two measures, we see that the $C_{a\text{-}p}O_2$ gradient is greatly elevated during hemorrhage. Because of inconsistent availability of flow probe readings on Day 1, we could not calculate the rates of delivery and uptake of oxygen in the gut in order to suggest which of the two is compromised. The oxygen extraction ratio, however, was seen to increase dramatically over the four hours of shock in Group II and Group III animals.

The mucosal hydrogen ion concentration increased during hemorrhage but this did not reach statistical significance. Given the changes seen in portal venous blood gases, however, it would seem reasonable that there should be a fall in gut mucosal pH during hemorrhagic shock.

During Day 3, several parameters showed differences in response to endotoxemia between animals which had previously undergone hemorrhagic shock, and those that had not. Aside from a trend toward acidosis (which did not reach statistical significance) in animals receiving endotoxin, arterial blood gases were not different between the three groups. This suggests that groups were comparable with respect to adequacy of

ventilation and oxygenation. A trend toward acidosis was noted in the portal venous blood of animals receiving endotoxin, but oxygenation of portal blood was not different among the groups.

The baseline hemoglobin concentration on Day 3 was notably lower in animals that had undergone hemorrhage on Day 1 than in those that had not. Possible causes of this trend include red blood cell injury during collection and reinfusion, and loss of small amounts of blood to tubing and collection bags. When corrected for differences in baseline, a significant increase in hemoglobin concentration was seen, and since no blood was administered, we may conclude that this represents hemoconcentration due to a shift of fluid from the intravascular to the extravascular compartment. This shift was greater in previously shocked animals (Group II) and could be due to an increase in permeability of capillaries which occurs to a greater extent in animals that have been "primed" by the first insult.

Since the P_aO_2 and S_aO_2 were held constant, the C_aO_2 during endotoxic shock reflects changes in the hemoglobin concentration. Again, although the baselines were different, statistical correction shows a significant increase of C_aO_2 in both groups of animals receiving endotoxin and a greater degree of increase in those animals that had previously undergone hemorrhagic shock (Group II). Combining C_aO_2 with the flow rate through the craniomesenteric artery allows calculation of the delivery rate of oxygen to the gut. In both groups of animals receiving endotoxin, an similar initial fall in DO_2 is seen. While this diminished delivery is sustained in the two-hit (Group II) animals, the one-hit (Group I) animals display a rapid recovery to levels greater than baseline.

The C_pO_2 demonstrated a significant increase in response to endotoxin which reflects the increase in C_aO_2. There was, however, no significant difference between animals that received endotoxin only, and those that received hemorrhage and endotoxin.

The C_aO_2 and the C_pO_2 were used to calculate the $C_{a\text{-}p}O_2$ gradient. Both groups of animals receiving endotoxin showed elevations of $C_{a\text{-}p}O_2$, but the two-hit animals developed a larger gradient than the Group I animals. In order to correct for differences in CAF rates, the rate of oxygen uptake by the gut ($V0_{2g}$) was calculated. While the endotoxin only animals (Group I) were able to increase their gut oxygen uptake, the previously hemorrhaged animals, when given endotoxin (Group II), decreased their VO_{2g}. Thus we see that despite preserved oxygen content of arterial blood, both delivery and uptake of oxygen by the gut were reduced in animals that underwent sequential hemorrhage and endotoxin stresses.

The sigmoid mucosal hydrogen ion concentration ([H+]) increased steadily during endotoxic shock. This is reflected in trends noted in the arterial and portal venous [H+]. While the trend did not quite reach statistical significance, the increase in [H+] in the previously hemorrhaged animals (Group II), was greater than that of the endotoxin only animals (Group I). This likely reflects the lowered oxygen delivery and uptake by the gut.

Serum endotoxin levels are elevated in response to endotoxin infusion in Groups I and II. While Group I animals show a brisk and sustained rise, Group II (hemorrhage and endotoxin) shows a greater peak level after the first 30 minutes (during which the infusion is given) which gradually falls toward that of Group I. Several possible explanations exist for this discrepancy. The difference could be due to the early liberation of endogenous endotoxin in addition to the exogenous infusion. Possibly there is a diminished ability of the animals to clear the infused endotoxin as readily as Group I. Another explanation is that the difference is an artifact due to reduction of the intravascular compartment size (as was seen with the hemoglobin levels). Without the use of isotope-labelled endotoxin, the truth is difficult to discern.

While both groups of animals receiving endotoxin displayed an increase in serum lactate level, this rise was slow and steady in the endotoxin only animals, but brisk and sustained in the previously hemorrhaged animals. This difference would tend to suggest a different response to endotoxin between the two groups. It would seem that the two-hit animals become dependent on anaerobic metabolism at an earlier phase in the shock than does the other group. This possibility is supported by the changes seen in delivery and uptake of oxygen in the gut which are likely reflected elsewhere in the organism. Conversely, a loss of ability to utilize lactate may be taking place.

In response to endotoxin, it is established that there is a mobilization of available hepatic glycogen with a resulting hyperglycemic phase which, if allowed to progress, is followed by hypoglycemia[207]. On Day 3, the endotoxin only animals (Group I), showed a small, delayed hyperglycemic phase followed by hypoglycemia whereas the hemorrhage and endotoxin animals (Group II) demonstrated a significant early hyperglycemic phase followed by hypoglycemia. This early peak in Group II might be due to enhanced hepatic glycogen mobilization by a system which has already been activated by the initial hemorrhagic shock. Conversely, it might be due to an inability to utilize glucose (insulin resistance). Elevated insulin levels later in endotoxemia have been sought by a number of investigators with varied positive and negative results[207].

A blunted cortisol response was anticipated in response to a second stressor, however, this was not seen. Instead, both groups of animals receiving endotoxin displayed the same gradual elevation of cortisol level as has been seen in other studies of endotoxemia[21,215]. This would suggest that after the hemorrhagic injury, the animal's hypothalamic-pituitary-adrenal axis recovers completely and is able to respond normally to endotoxin, but the target organs which regulate measured parameters already mentioned, respond differently to the cortisol (and other stress hormone) surge from the second metabolic challenge.

V. Bacteriology

At the onset of the study, bacterial species commonly isolated from swine were assigned to positive (typically gut-derived) and negative (contaminant) groups in accordance with previous studies of this nature. In reviewing the results of bacteriologic study of the experimental animals, the high prevalence of contaminants must be addressed. There are two possible causes of contaminated samples. They could represent technical errors in obtaining sterile samples of blood from the indwelling catheters, and tissues from the opened animal during the second laparotomy on Day 5. Alternately, there may have been environmental contamination due to inoculation by way of skin or respiratory tract secondary to intravascular catheters and endotracheal intubation. In support of these explanations is the fact that, contaminants in blood cultures were always isolated, transient events which did not persist in subsequent samples. Contamination occurred in spite of precautions taken to collect samples in a sterile manner. These included dissecting and removing each tissue sample with a fresh, sterile forceps and scissors. Tissues were cultured several hours after retrieval because of delivery time to the laboratory. The fact that several specimens grew *Clostridium perfringens* (which are sensitive to condition and delay) suggests that organisms were well-maintained within the tissue samples from the time of collection to the time of inoculation into culture medium. Possibly, the intestinal flora of the animals could have been characterized in order to document which organisms isolated from normally sterile sites were truly contamnants and which were gut-derived. Characterizing the full range of organisms in stool, however, would have added great expense to the study and would be of doubtful relevance.

The central reason for bacteriologic analysis was to determine if the profile of organisms translocated from the gut 48 hours after a physiologic stress (endotoxin) was

any different if a previous stress (hemorrhagic shock) was also administered. Our results suggest that there is.

Firstly, half of the two-hit animals (Group II) developed pathogen-positive blood cultures after the second insult whereas non of the one-hit animals did (Tables 138, 139, 140). Second, while almost all lymph node cultures were positive for pathogens, the profile of bacteria was different in the Group II animals with *Enterococcus* cultured in 2 of 6 animals' nodes while none was seen in the one-hit animals (Tables 142, 143, 144). Solid organ cultures also showed a significantly greater prevalence of infection with *Enterococcus* in Group II animals (Tables 146, 147, 148). *Enterococcus* is recognized as a significant pathogen for causing organ failure and mortality in critically ill patients, especially when it exists as part of a polymicrobial infection[201,216]. It has also been isolated more frequently than E coli or P. mirabilis from MLNs of rodents thus suggesting either that it translocates more readily or that it is more virulent[217]. Third, Group II animals also displayed the highest total number of positive solid organ tissue cultures and polymicrobial cultures.

Of note is the frequency with which positive tissue cultures are seen without concurrent positive blood culture. This suggests that in the critically ill patient, blood cultures may not adequately reflect the bacteriologic profile of the patient's septic state.

CONCLUSIONS

It has now become well-established in the literature on Multiple System Organ Failure that the gastrointestinal tract with its infectious and toxic contents plays a pivotal role in the genesis of this syndrome. A variety of physiologic stresses have been shown to be capable of bringing about translocation of bacteria and bacterial toxins from the gut into the mesenteric lymph nodes and, under conditions of sufficient ongoing stress, into parenchymal organs and systemic blood. The understanding of this process bears further investigation as its prevention will save suffering, lives, and resources.

Current thought suggests that an initial injury such as trauma or surgery may permit bacteria and endotoxin to escape from the gut into mesenteric lymph nodes and, from there, incite activation of the systemic inflammatory mediator cascade. In most cases, the gut barrier recovers and the inflammatory mediator activation is extinguished by normal homeostatic mechanisms. In cases of a secondary injury, usually in the form of a delayed infectious challenge, the mechanisms of recovery are confounded and a malignant inflammatory response is activated which may bring about failure of organ systems, including the gut.

The results of this experiment, indeed, raise more questions than they answer. If gut bacteria and endotoxins are the cause of the priming of the host, or the amplified response to a secondary stressor, or both, should attempts be made to reduce or alter gut bacterial populations of pathogenic organisms? Clinical studies of this intervention in critically ill patients have met with mixed results. Since inflammatory mediators seem to play a role, should intervention be sought to suppress this inflammatory response? If this were done, would the subject not then be left in an immunocompromised state which

would allow further infectious complications? Current research hopes to selectively suppress 'harmful' aspects of the cytokine cascade. It might be wise to assume, however, that the teleology of man is such that the inflammatory system has developed its present state of balance and responses to optimally serve the host, and that it is best not tampered with. Instead, the focus of attention might better be drawn toward the reduction of the stresses which cause activation. Early, adequate resuscitation, debridement of devitalized tissue, fracture fixation, strict asepsis in dealing with indwelling catheters and drains, early drainage of infected and potentially infected collections, pain control and adequate nutrition represent clinical interventions. In the laboratory, exploration of anti-endotoxin antibodies, lipid X, and pharmaceuticals which would aid in recovery of gut barrier function should be sought. The bacteriologic results of this experiment also draw attention to the role of *Enterococcus* in the critically ill patient as well as the importance of tissue sepsis in the absence of bacteremia.

As with any animal model of experimental stress, there are differences between our laboratory animals and critically ill or injured humans. The fact that the animals were anaesthetized during shocks presents a confounding factor as does the fact that the shocks administered were of different severity and duration than what is commonly encountered clinically. The lack of gut rest in these experiential animals might also play a role. One might criticize the decision to deliver the first insult on the same day as surgery, thus arguing that two insults were given. The decision to administer endotoxin by way of the portal vein might also be argued.

It has been the purpose of this study to examine this theory of priming and activation of the inflammatory response and the failure of the gut barrier that results from injury. More specifically, the question is asked whether or not an initial injury sets up a condition in an animal (being a model of man) such that a second insult would bring about a response different from that which is typically seen in cases where the first injury was not

administered. With certain qualifications, the answer to this question is yes. The data obtained in this experiment suggests that differences do exist in terms of hemodynamic, biochemical, and bacteriologic changes brought about by some form of priming with subsequent activation. This information gives support to what has become known as the two-hit theory of MSOF.

RECOMMENDATIONS

Sepsis and multisystem organ failure continue to be the major causes of late morbidity and mortality in traumatized and critically ill patients. As with other obstacles in the path of the advancement of medicine, these will eventually be overcome, but not without further understanding brought about by the continuation of projects such as this one. Bearing in mind the conclusions that have been made in support of the two-hit theory of MSOF, the following recommendations for further research are offered:

1. Further understanding of the mediators involved in the response to sequential insults is required. This would then give direction to efforts to abate the response and prevent its consequences. Specific measurements which could be made include:
    a. tissue levels of endotoxin in liver, lungs, kidneys, heart, brain, gut and lymph nodes.
    b. measurements of changes in circulating levels of TNF, PAF, interleukin, cyclo-oxygenase and lipoxygenase products, nitric oxide, and catecholamines.
    c. response to suppression of particular cytokines using antibodies (to TNF and PAF) or enzyme inhibitors (NSAIDs, steroids, interferon, 5'ASA)
2. As the gut is the source of toxins and pathogens believed to be responsible for MSOF, enhancement of gut barrier function through enteral and parenteral glutamine supplementation could be explored. Also, the effects of a reduction in the populations of pathogens in the gut through selective decontamination with antimicrobials could be reviewed.

3. The impact of improved oxygen delivery to the gut during stress, by means of selective splanchnic vasodilators, could be investigated.

4. It is hoped that this work will have applicability to humans. Continued efforts should be made to demonstrate gut-derived septic states in patients.

5. Given the physiologic similarities between humans and swine, the model used in this experiment was felt to be quite adequate. Still, improvements could be made:
    a. The experimental period should be lengthened to allow further development of organ failure and sepsis.
    b. Gut rest (starvation) should be given (with oral and IV fluids only) to further simulate the critical care situation.
    c. Stool cultures should be obtained before and after experimentation.
    d. Improvements should be made in culture collection techniques in order to reduce contamination.
    e. Intravascular catheters and catheter care should be modified in order to reduce the risk of contamination of blood from this source.
    f. Experimentation should be carried out on an awake animal.
    g. The first physiologic insult should be given 1 week or more after surgery for placement of catheters and flow probes. This would allow full recovery before adding to the stress of surgery.

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